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SPEECHES AND ARTICLES BY/ON DR. JAMES A. SHANNON

Volume III

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Guest Editorial

Rehabilitation: New Needs And New Opportunities

—NIH Photo

JAMES A. SHANNON, M.D., has been director of the National Institutes of Health, Bethesda, Md., since 1955. Recipient of the 1965 Rockefeller Public Service Award, Dr. Shannon is widely recognized in the scientific world for his original research in kidney function, chemotherapy, and malaria.

THE ADVANCES in medical research and practice which in the past half century have led to great saving of lives and lengthening of life have left almost untouched the rehabilitation of those disabled by accidents and by physical and mental disease. Indeed, many of the life-saving advances have increased the problem as they have added to the numbers of the living but disabled who need rehabilitation.

This is not to say that there has been no progress, nor yet to belittle the efforts of those dedicated men and women who have made great strides in advancing both the concepts and skills of rehabilitative therapy. The growing realization of the vital need to initiate appropriate rehabilitation procedures immediately after diagnosis of the acute condition or accident—often during the medical treatment itself—is but one of the results of these persons' efforts.

However, just as a great deal of our progress toward improving health has resulted from and been based on greater knowledge of fundamental biochemical and biophysical processes, so it would seem that further progress toward rehabilitation of the disabled from whatever cause may be expected to come from similar investigation of fundamental processes in the disabled. For example, suitable physical exercise may restore some degree of strength to weakened muscle tissue, but one might hope that greater knowledge of biochemical and biophysical changes associated with the process of muscular atrophy could lead to more definitive means of stimulating restoration of function.

Yet we need not await further development of knowledge through research to improve the condition of many of our presently disabled men, women, and children. *Our immediate task is to bring current knowledge and skills to larger numbers, and to people in all regions.*

Presently, great advances can and are being made, for example, in treatment of victims of heart disease, cancer, stroke, and mental illness. But the necessary skills, equipment, and facilities are available in only a few large centers and to only a few of those who might benefit from the newer diagnostic, therapeutic, and rehabilitative measures.

To speak of the rehabilitation of victims of mental illness still seems strange to too many people. The popular image of rehabilitation remains as one consisting largely of physical aids to mobility and use of arms and legs, of acquisition of new vocational skills, and of new methods of performing ordinary physical tasks involved in routine daily activities. Modern practice of rehabilitation, however—as *Journal* readers know—involves more subtle and significant, if less obvious, psychological factors. And rehabilitation of recovered mental patients has pioneered a facet of rehabilitation which soon will be followed in rehabilitation efforts for recovered victims of heart disease, cancer, and stroke.

I refer here to the concept of community centers throughout the nation which can make available to people near their own homes the best in modern diagnosis and therapy of all kinds. The large custodial institutions of the past—somewhat misnamed as mental hospitals—are giving way to small, community day-and-night hospitals, clinics, and half-way houses where the mental patient is given psychotherapy and, as early as possible, the opportunity to return to his home and community life.

Now steps are being taken, as part of the implementation of the recommendations of the President's Commission on Cancer, Heart Disease, and Stroke, to follow this lead toward community centers or complexes which will make available in every region, instead of in just a few centers, the most modern facilities and skilled professional staffs for diagnosis and therapy of victims of these leading killing and disabling diseases. In addition to their diagnostic and therapeutic activities, these new complexes will also serve: (1) as centers for training physicians and other professionals in both the best presently known methods and in future ones as they become available; and (2) as centers for research in cancer, heart disease, and stroke.

Here, then, lies the future for rehabilitation, using that word in its very broadest and deepest sense.

J. A. Shannon

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NIH-OD-OPP

THE NATIONAL SCIENCE FOUNDATION--ITS ROLE AND RELATIONSHIPS TO OTHER FEDERAL RESEARCH PROGRAMS

Statement by James A. Shannon, M.D.
Director, National Institutes of Health
Before the Subcommittee on Science, Research, and Development
House Committee on Science and Astronautics
July 14, 1965

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

I am grateful for your invitation to participate in this review of the National Science Foundation. I will be happy to describe for you the relationships between that organization and the National Institutes of Health, and to give you my views on what the further role of NSF should or might be.

I particularly value this occasion because I recognize that whatever conclusions are reached here about the present and future role of NSF will have an impact on all other science programs, including those of NIH. The fabric of National Science Foundation programs cannot be reshaped without setting up new lines of force, that--for better or worse--will affect the ability of Federal agencies to accomplish space, health, defense and other missions requiring a broad scientific base. Nor can one ignore the possible impact upon our national structure for the support and advancement of science as the concept and functions of NSF change. In a very real sense the National Science Foundation occupies a central position in that national structure. To the extent that one redefines the characteristics of this central agency, then

one must look to the total Federal science structure to determine what further modifications will have been made necessary.

A second reason for wanting to talk to you is that in my years of administering health-oriented programs that touch and interrelate with NSF at innumerable points, I have formulated some personal but quite definite opinions about what the role of NSF in science should be. I will confess at once that you will find nothing original or startling in my views. Others have advanced the concepts earlier--and doubtless more eloquently--than I. My recommendations merely reiterate those you will already have heard. But the perspective--or if you will, the bias--from which I speak will be very clear to you; and the length of that personal perspective (some ten years during which NIH and NSF have both had their maximum growth rate so far) may add at least an element of interest for you.

What I propose to do is as follows: I will first try to capsulize for you the nature of present NIH activities, how they got that way, and how--through time--they have interrelated with programs and responsibilities of NSF. I will also describe several joint NSF-NIH efforts in common problem solving. I will then discuss my view of the present role of NSF in science and science education, and what I feel are important considerations relating to the future.

The Nature of NIH Activity

The National Institutes of Health has, as its primary mission, an understanding of disease and of the behavioral and biological requirements for health. In the furtherance of this mission, NIH has come to play a major role in the support of research in institutions of higher education in our country. Thus it now has an indirect though major role in strengthening graduate education as such and in adding to the vigor of the institutions which largely contain these research programs.

From the beginning it was recognized that effective support for research carries with it the obligation to enlarge the resource base for continued growth in the future. As a consequence, NIH programs have provided fellowships, have strengthened the structure of graduate education in health-related fields, have provided stable support for faculty expansion, and have stimulated the construction of health research facilities through a matching grant program. This broad spectrum of biomedical research and research-related activities has drawn the National Institutes of Health into close and increasingly fruitful relationships with educational institutions. We have become increasingly aware of the capabilities of Federal programs (1) To support research and, at the same time, to strengthen rather than weaken the educational enterprise, and (2) To broaden the Nation's base of biomedical excellence in all regions of the country.

Background of NIH Development

Some comment on the background of this activity may be helpful in understanding the character of present NIH involvement in scientific activities. To shorten this story I will utilize three key years: 1945, 1950, and 1965.

In 1945, as World War II ended, the creation of the National Science Foundation was still five years away, though Vannevar Bush and others were urging the need for such an agency. In that same year, NIH was in its 59th year as the research arm of the Public Health Service. Essentially, then as now, NIH was a health agency using science as a means to accomplish its objectives. The basic authority for NIH programs derives from the statutory responsibility of the Surgeon General of the Public Health Service for the conduct and support of research and investigations related to the diseases and impairments of man and other health problems. The general authorization for this purpose appears in Section 301 of the Public Health Service Act. In 1945, however, the tangible attributes of NIH were those of a small in-house Federal laboratory. Less than 6 percent of its funds went to support university scientists, and its total budget was less than $3 million.

But in the circumstances of that year--and especially what had grown out of the war years immediately preceding--were all of the essentials for a vast build-up in Federal science support programs. At least in tentative form, the pattern for future NIH expansion was also present:

. . . There was both the identification of major medical problems and an appreciation that the then current state of the art required a broad extension of basic science for their solution.

. . . There was also clear evidence of a successful wartime partnership between the Government and university science in concentrating scientific effort in needed areas.

. . . There was the effective policy and administrative framework for implementing this partnership that the Office of Scientific Research and Development has worked out.

. . . The National Cancer Institute, added to NIH in 1937, set the pattern of later expansion through creation of separate disease-oriented Institutes.

. . . The Public Health Service Act of 1944 gave broad authority for grant support of extramural research projects.

—Finally, the 1946 transfer to NIH of the residual OSRD university contracts in the medical sciences constituted the effective beginning of NIH's present day broadly based extramural research support program.

By 1950, however, a considerable shift had taken place on the national science scene. In that year, in which creation of the National Science Foundation was authorized by Congress, major research support programs of the AEC and Office of Naval Research were well underway. Seven of the nine research Institutes which comprise the present day National Institutes of Health had been authorized and their programs launched. In 1950,

NIH spent $28 million for research--roughly half going for support of research through grants to academic and research institutions throughout the country. NIH training grants programs were then in their third year; and NIH appropriations for 1950 included $6.4 million for these grants plus $1.4 million for fellowships. Thus by the time the legislative authorization for the National Science Foundation had been completed by Congress, the Federal Government was already heavily involved in the support of academic sciences through the postwar development of the mission-oriented Federal agencies. By reason of this somewhat accidental set of circumstances, the basic pattern was forged for the Federal engagement with science in this country.

Since 1950, NIH appropriations have grown steadily until they now (1965) total slightly more than $1 billion. Although the intramural research activities on the Bethesda campus have grown steadily, the extramural programs have expanded at a much more rapid rate, with the increases being particularly striking during the past decade. Expenditures through extramural programs for research, training, and construction grants now account for nine-tenths of the NIH dollar. As a consequence of this progressive and rapid growth, NIH funds now cover 40 percent of total national expenditures for biomedical and health-related research; also more than one-third of Federal research funds made available to institutions of higher education. Thus at the present time NIH has a substantial investment in university research, and,

therefore, a basic concern with their capabilities for productive research as well as for their further growth.

Science as a Means Rather Than an End

This extensive NIH involvement with academic science and its institutions--though NIH is not primarily a science agency--does not make NIH unique. This, in fact, has become the hallmark of this country's engagement with science at the Federal level. In contrast with the pattern in a number of major countries--where the support of science is approached directly and as a primary consideration--the advancement of basic science in the United States has been in very large part the derivative of national efforts to achieve non-scientific goals: in agriculture, in national defense, in communications, in health, and other areas. Though there is room to argue the wisdom of this pattern, one cannot say that the results have been bad. For example, one may speculate--with some confidence--that the scope, the magnitude, and the general excellence of academic science is undoubtedly greater today (as a consequence of efforts directed toward national objectives in the areas of health, defense and space exploration, etc.) than could be expected on the basis of seeking support for science primarily for its own sake. There are many strengths in this situation and I believe this will continue to be the pattern for some time to come. However, there are problems of overall balance across fields of science; there is also the need to advance science education generally, and to assure

the resources and development of institutions essential to that advancement. These circumstances make critical the need for a total Federal pattern within which academic science as a whole can be dealt with adequately. In this setting NSF has a crucial role.

NIH-NSF Cooperation

I should like to take a moment at this point to review for the Committee the nature and extent of specific NIH-NSF relationships.

In the development of its programs, NIH has worked continuously and closely with NSF. Collaboration has extended to specific scientific studies; to working out generally comparable terms and conditions of support for research, training, fellowship and facilities programs in similar settings. The two agencies employ basically the same concepts in respect to the peer group review system for academically based research. There is now a growing concern for coordinating activities and programs which focus upon the same institutions.

I cite below a few instances of this cooperation:

Research and Training Grants

Representatives of NSF are invited to attend all NIH National Advisory Council meetings. The Executive Secretaries of the various NIH Study Sections and Training Committee panels maintain close informal contact with program officials of NSF in coordinating action upon proposals from the same investigators and in areas of common interest.

This information exchange is useful to both groups and also avoids inadvertent duplications. There is joint funding in the case of large programs of common interest. Applications received at one or the other of the two agencies which fall outside of the recipient's support area or interest are referred to the other Agency for possible funding. As an example of cooperation in more specific program areas, NIH is included in the Interagency Chemistry Representatives, a group that meets twice a year under NSF auspices to discuss common problems in support of chemistry.

Facilities

The NIH Division of Research Facilities and Resources has continuing interchange between its facilities program officers and their counterparts at NSF. This interchange is particularly active when there is need to work out joint funding arrangements for the construction of facilities at particular universities. A representative of NSF sits as a non-voting member with the National Advisory Council on Health Research Facilities when construction proposals are reviewed.

Fellowships

Semi-annual conferences of Federal Fellowship Program Administrators are held under NSF auspices. At these meetings, common policies on stipend and support levels are negotiated; there are also informal discussions on delineation of respective scientific spheres, problems of projections, etc.

Data

In the development of resources data, NSF surveys have been expanded to provide the greater detail needed by NIH, especially for the biosciences. In such instances as the 1960 Survey of Foundations and this year's Survey of Research Institutes, the Science Foundation has added a separate sheet for medical and health-related activities; this is made available to the National Institutes of Health for analysis and publication. Also, the National Science Foundation maintains the National Register of Scientists and Engineers through the use of biennial questionnaires. Decks of IBM cards from this roster are made available to NIH when the need is indicated for more detailed analysis in fields of specific NIH concern. NSF has also provided NIH with a deck of IBM cards covering the responses of institutions to its Survey of Research Facility Requirements, 1962-70. NSF and NIH frequently cooperate in financing contract studies or surveys relevant to scientific manpower, graduate education, and university activities of common concern. These illustrate only a few of the many and continuing relationships that exist between NSF and NIH. This interchange and common action has been cordial, productive and mutually contributory to the advancement of our respective programs.

View to the Future

From the perspective of an agency supporting science to accomplish non-scientific, social objectives, what should be the future NSF role in support of science?

In brief, I would say: not too different from what it is now and had been in the immediate past. I say this reflecting my conviction that the Federal structure erected for the support of science since World War II has been, on the whole, outstandingly successful; and that it still appears essentially sound.

The main program strengths of NSF [illegible] relate to the distinctive, explicit and primary concern for the advancement of science assigned to NSF. These are: the support of basic science research, the enlargement of scientific and technical manpower and advancing the institutional structure and resources for science and science education: and the doing of these things without the restriction of a substantive mission. I believe that NSF should be so funded that it can assure world leadership for the U.S. in the future course of scientific development. Inescapably this would mean that NSF should be funded generously to fill meaningful gaps and deficiencies in the science structure left by mission-oriented agencies such as AEC, NASA, Defense, NIH, etc. It should not, however, be limited to this role. The NSF function in measuring and analyzing the quantitative and economic characteristics of science and its resources is basic to formulation of programs and policy. Its concern with the crucial role of science as a national resource, as an instrument for strengthening international relations and--in a quite literal sense--as the determinant of the destiny of man, must be reflected in the scope and magnitude of its activities. These views, you will note, are generally in accord with consensus on the functional concept and the

"balance wheel" role for NSF advanced in the recent study by the National Academy of Sciences.

I trust that in what I have said above I will not be understood to be urging adherence to status quo precepts for their own sake, or because they generally are favorable for a particular agency. On the contrary, it is the flexibility and capaciousness of the present science structure that I value and would like to see carried into the future.

As a final consideration I would like to emphasize an important point with respect to the present distribution of Federal support for science and related activities which should stand clear to the committee and the Congress in the further pursuit of this inquiry. For this purpose we have prepared a chart (included in the copies of the testimony before the committee) which portrays three aspects of Federal expenditures for research and development:

The first pie diagram shows the proportionate distribution of total 1965 Federal expenditures of $15 billion for research and development amongst the major Federal agencies involved. The inclusion of the large-scale expenditures for hardware development contributes to the dominant positions of the Department of Defense, NASA and AEC in this presentation. NSF, NIH and other DHEW agencies whose programs are centered in research rather than development account for only 7 percent of the total Federal R&D activity.

In the second pie diagram the focus shifts to that portion of Federal R&D expenditure--approximately $1 billion--comprising Federal support of research in educational institutions. This excludes the large university associated research institutes such as the Jet Propulsion Lab at Cal Tech and the Lincoln Lab at MIT. This is the area of support for academic science and encompasses the major portion of the total national support for basic research. In this context the proportionate roles of the several Federal agencies shift markedly: the National Institutes of Health--constituting 36 percent of total--emerges as the Federal agency supporting the largest proportion of academic research. NIH, together with NSF, the Office of Education, and other DHEW agencies accounts for over one-half of all Federal support for research in academic institutions. The critical role of NIH and NSF in sustaining academic science is clearly apparent.

In the third pie diagram, the focus on educational institutions continues. However, the data not only show support for research in such institutions, but Federal expenditures for training and for construction of teaching and research facilities as well. This expenditure is estimated at $3 billion dollars in FY 1965. Here the role of the Office of Education in the support of training and the construction of academic facilities shows its effect. Altogether the activities of NSF, NIH, OE and other DHEW agencies comprise 65 percent of the Federal funds going to educational institutions for training, research and construction. Given the growing dependence of institutions of higher learning upon Federal support, the

crucial role played by NIH, NSF and the OE in the destiny of the national structure for higher education is emphasized by these data.

This concentration of Federal support for academic sciences in the programs of three agencies has obvious relevance for this committee. I should also like to depict briefly a set of considerations that I feel are integral to your concern with the National Science Foundation:

1. Although the Office of Education occupies a dominant position in the support of training and the construction of educational facilities, its role in the support of the substance of science remains minor as shown by the second pie diagram.
2. Thus NIH and NSF occupy a critical position in support of university research, particularly in face of declining DoD expenditures in this area.
3. The further growth of NIH as an agency concerned with the solution of major disease problems will involve positive efforts to provide movement along two fronts:
   a. An increased extension of the advances in basic science and technology to the specific problems of the major diseases through applied and developmental activity.
   b. Broad efforts to bring the physical, behavioral and mathematical sciences into more intimate involvement

with the biomedical sciences in the provision of stable base for the applied effort.

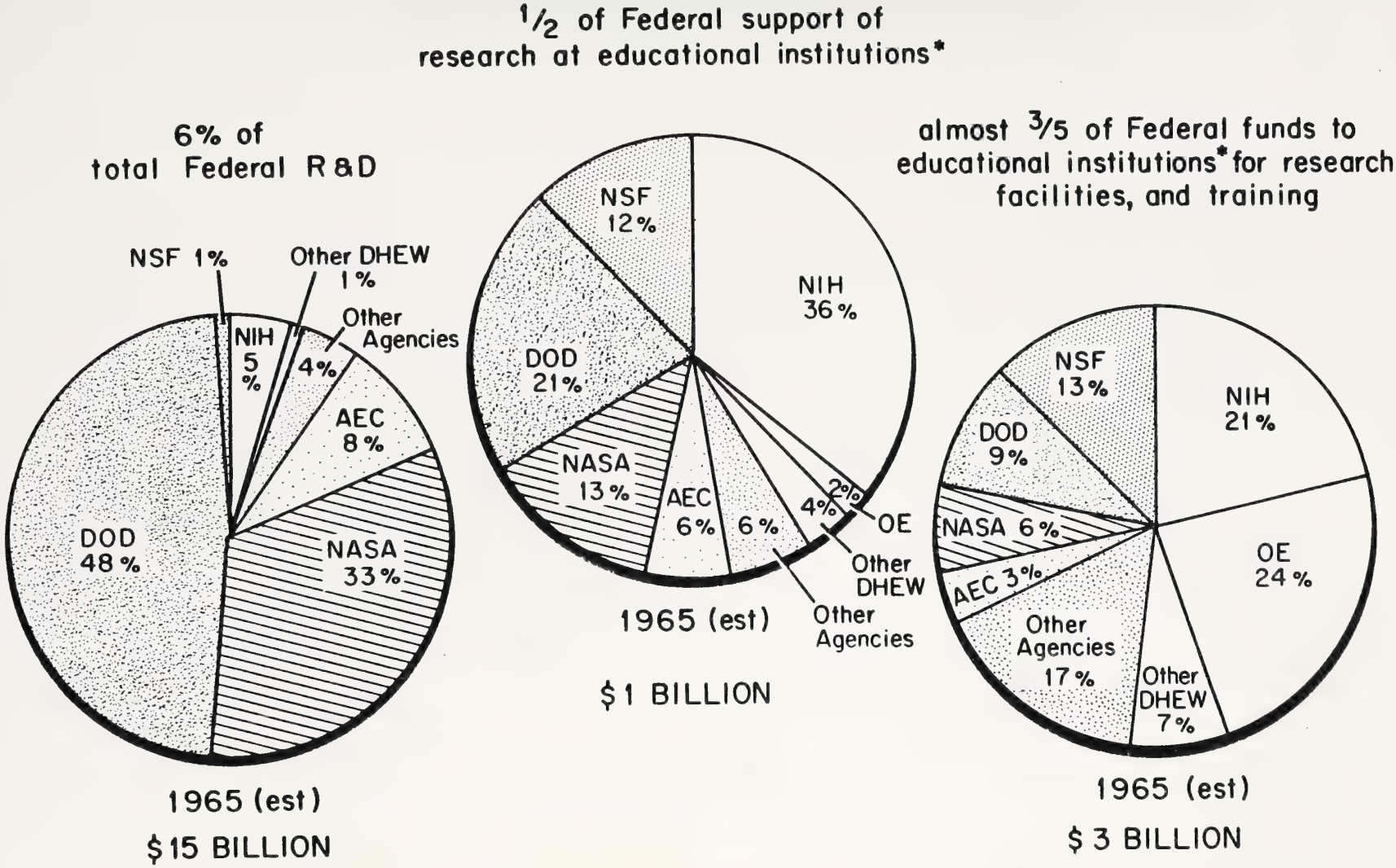
Great care will be required of administrators and legislators in the furtherance of this dual process to avoid distorting an existing balance between that which is fundamental and that which is applied or bringing one into conflict with the other.

4. Somewhat comparable problems will be presented to NSF. National circumstances will require continuing involvement of NSF in the direction and management of large scale science projects such as Mohole, radio astronomy, and weather modification. This involvement is sound in terms of the importance of these projects for science and science education generally. But it will continue to be sound only if NSF can direct ever increasing resources to its pivotal role and imperative function of providing for the stability, vigor and growth of academic sciences generally.

These comments, I believe, define essential relationships between these agencies which--although quite different in origin, purpose and role--have been able to accommodate the development of their programs in a mutually reinforcing manner. As I noted at the beginning of these remarks, modification in one agency vitally affects the other.

These are matters which will benefit, I know, from the constructive deliberations of this committee. Thank you for the opportunity to add my thoughts in this important examination of an agency which in 15 short years has become indispensable to the national welfare.

NIH - OE - NSF ACCOUNT FOR .....



*Excludes university-managed Federal contract research centers.

SOURCES: Office of Education, National Science Foundation, National Institutes of Health.

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TAB 57

Testimony by
Dr. James A. Shannon,
Director, National Institutes of Health,
before the
Subcommittee on Patents, Trademarks, and Copyrights
of the Senate Committee on the Judiciary
August 17, 1965

Mr. Chairman and Members of the Committee:

I appreciate the opportunity afforded by your invitation to appear before this Committee and discuss the relationships of patent policies to NIH programs, especially as it concerns research financed by multiple sources or situations where additional private funds are necessary for the full development of an invention. At the outset, I would emphasize that the NIH, as one of the bureaus of the Public Health Service, is a component of the Department of Health, Education, and Welfare, and functions within the patent regulations set forth by the Department.

I understand that the Department's patent policies and its position on the legislation before this Committee have already been presented. For this reason, I will limit my statements to the two areas of concern mentioned in your invitation.

I would first like to address myself to situations where additional private funds are necessary for the development of an invention made under Federal support, since I believe the policy problems attending these situations are a major public concern.

The NIH supports research activities through grants, contracts, and within its own laboratories which may result in the discovery of

potential therapeutic agents. Before one of these agents can reach the marketplace for public consumption, it must travel a long road, usually measured in years, from discovery to complete development. This road includes the actual discovery of the potential therapeutic agent, the preliminary screening to determine if the agent has possible therapeutic usefulness, different stages of animal testing, preliminary tests in humans and, finally, full-scale clinical testing of the agent. The newly discovered agent may be a completely new chemical entity or an old chemical either of which is shown to be useful as a therapeutic. The developmental process in either case is governed by the Federal food and drug laws which require evidence of careful testing before the agent can be cleared for the market.

In most instances the NIH or its grantees do not participate in the full development of a therapeutic agent up to the point where it is made available commercially. We view our role in the Nation's medical research effort as complementary to the activities of the other elements within our society, both public and private, that also support research and development related to health. It seems to us that the interests of the American people are best served when the various elements of this medical research structure can interact. The most effective interrelationship results when the particular capabilities of the various elements, Federal and nonfederal, can be utilized to the fullest extent.

Generally speaking an NIH scientist or grantee will be involved, if at all, at one of four points in the developmental process:

a. NIH funds may be involved in the organic synthesis of a compound and perhaps in a portion of its screening in biological systems. He may participate in animal and clinical testing but will not usually, except in psychopharmacology and cancer chemotherapy, pursue this to a definitive conclusion.

More generally the chemist, given freedom of action, would approach the pharmaceutical industry which has extensive capability to undertake the entire development and testing process and is able to accumulate all the data from different stages of development necessary for FDA acceptance.

b. NIH funds may also be involved in support of research which involves the probing of biological mechanisms with chemical agents. Out of such investigation may well come new knowledge on novel uses for a compound, but in general such an investigator will rarely have the capability of follow-through as with a wholly new therapeutic agent.

c. NIH funds more recently support broad clinical investigation and such work has a heavy commitment to the assessment of therapeutic activity either in absolute or comparative terms. Out of this type of work in the past has come wholly new therapeutic uses that have had broad impact on clinical medicine. I have in mind in this respect the discovery of tranquilizing properties of reserpine when this drug was in use as a blood pressure lowering agent and the discovery of energizing properties of isoniazide when the drug was being explored as an antitubercular agent.

d. Finally, NIH has, in the past, supported and/or participated in the extensive type of field trial which firmly establishes the net benefit to be derived from a given compound under well-defined clinical conditions, and will no doubt do so in the future.

The first three of these types of studies can be expected to yield patentable discoveries and consequently the rate of evolution to an effective therapeutic agent generally available to the public will be determined by the terms and conditions which facilitate the interplay of the resources of the Federal Government, the university scientists and the pharmaceutical industry.

Although NIH support of an investigator may stop at an early stage of development or cover only a part of the complicated sequence of drug development, our Departmental patent policy requires that his invention be reported to the Surgeon General for his disposition since the invention in most instances is complete within the definition of the U.S. Patent Office. The Surgeon General's disposition generally results in title to the Government in accordance with the provisions of the Department's regulations, the title provisions of the President's Memorandum and the Executive Order governing disposition of employee inventions.

The uncertainties involved in after-the-fact determinations have created barriers for collaboration by the drug industry with NIH-supported scientists in bringing potential therapeutic agents to the point of practical application. The industrial firms want some guarantee of

exclusive patent rights as compensation for and protection of their possible investment, which may be considerable before FDA clearance can be obtained. Because, as I understand it, there is some question as to whether we can or should extend such a guarantee, it is often difficult to motivate industry to undertake the perfection and marketing of the NIH-supported inventions.

We, of course, support the basic policy that title to health and welfare inventions generated primarily with Federal support should reside in the Government. It does seem to us as persons responsible for the largest Federal medical research program that there does need to be clarification of the situation with regard to the issuance of licenses to inventions held by the Government. One possible solution might be the granting of short periods of exclusivity in such situations as I have discussed--that is, where it is found to be necessary to develop an invention to the point of practical application and there is no other way to obtain the needed industry cooperation. Compounds which show some promise in early stages of investigation may be of no benefit to the public and may not serve the public interest unless clinical testing is undertaken and the resulting drug is cleared by the FDA and marketed. We also believe that it seems sensible to be able to involve industry in the testing and marketing phases of drug development since these firms already possess capabilities in these areas that would have to be duplicated elsewhere to accomplish these necessary purposes.

The Department is in the process of reviewing its entire patent policy and practices.

Passing on now to the second area on which you wished my comments, I would note that one of the common characteristics of scientific research activities performed in universities is receipt of joint and simultaneous support from Government and nonprofit organizations, and not infrequently from industry. In the biomedical sciences, the Government support is most frequently provided in the form of a grant from the NIH. Funds from these different sources of support are often commingled with the result that a given research project may be financed and dependent upon several different sources of income at the same time. Where the private sources of support impose no conditions upon their grant relating to inventions, the DHEW regulations requirement that the NIH grantees report all their inventions to the Surgeon General for his disposition poses no problem. However, where, as in the case of the American Cancer Society and the American Heart Association, co-sponsors maintain patent policies requiring their grantees to agree to assign all invention rights to them, the grantee who accepts support for the same research activity from both the NIH and such other sponsors has undertaken conflicting obligations he cannot fulfill. It is difficult to solve problems of conflict after the fact on the basis of priority as between the co-sponsors. Neither is it a satisfactory solution to suggest that the grantee be limited to acceptance of support from only a single source which imposes such an obligation.

I believe it is in the public interest to encourage support of research from the private sector of our economy and to discourage exclusive reliance upon Government-financed support. In order to further this objective, it may be necessary to relieve universities and their researchers from the dilemma created by conflicting obligations to assign patent rights.

At the present time, it is my understanding that the patent regulations of our Department do not take into consideration the equities of co-sponsors in making disposition of inventions arising from research financed by multiple sources, and the Surgeon General must make his determination solely on the basis of our support. As I have mentioned, I do understand that these regulations have been under review for some time with this matter being given consideration by the Department.

Thank you very much for this opportunity to appear before you. I would like to emphasize that I am obviously not a patent expert, but I would be glad to answer any questions from my perspective as the director of a large Federal research activity.

Statement by
Dr. James A. Shannon
Director, National Institutes of Health
before the
Subcommittee on Public Health and Welfare
House Committee on Interstate
and Foreign Commerce
Thursday, September 30, 1965

Mr. Chairman and Members of the Committee:

I am pleased to appear before you today to testify on legislation concerned with the care and treatment of animals used in research.

This Department, as one of the principal Federal agencies conducting and supporting health and medical research, is fully aware that the humane care, handling, and treatment of laboratory animals is not only necessary to maintain the high quality of laboratory animals needed for medical research purposes, but is a moral obligation of a civilized society. We believe that this concern for the humane treatment of laboratory animals is only a logical extension of our general mission in protecting and improving the Nation's health.

No one can consider the great strides made by modern medicine in preventing human death and alleviating human suffering without a strong sense of appreciation for the truly humane work of our medical scientists. The list of great medical accomplishments is familiar to us all. In a single area such as the cardiovascular field, one can take note of a number of striking advances which now prevent or ameliorate serious disability and early death. I have in mind the broad advances in vascular surgery, heart surgery, including the complex procedures involving the open heart, development of the artificial kidney, management of

major trauma and shock such as one sees in serious accidents and war injury, development of a wide range of therapeutic agents including drugs for the lowering of blood pressure, anti-coagulants, and many others. This Nation has mounted the greatest medical research effort in history, largely stimulated by actions of the Congress and this Committee, for the purpose of making further advances against those diseases that have not yet succumbed to the determination and ingenuity of the medical scientists.

Most if not all of these medical advances, past and future, have in common their dependence on the use of a large number of animals in research. While this fact is obvious, we believe that it is important to keep in mind the ultimate purpose of these research activities in order to provide perspective for the matter before the Committee. It is our view that proper care and treatment of laboratory animals can best be considered as an integral part of the conduct of medical research. Just as there must be a justifiable purpose for utilizing animals in research, so the use of laboratory animals must not be considered without reference to the research purpose.

Using this perspective, the Department looks on laboratory animals as a vital and basic resource for the conduct of medical research. As such, their care and treatment deserves the same effort and careful attention that is devoted to the development of other essential resources for high quality research--such as trained manpower, facilities, equipment, and information systems.

In recognition of the problems associated with providing adequate care for laboratory animals, the Public Health Service has taken a number of constructive actions. In the first instance, NIH has utilized its position as the largest

biomedical research institution in the world as a model for the study and care of laboratory animals. The array of facilities and resources of the National Institutes of Health has been helpful to many others in the design, construction, and maintenance of animal facilities and the care of laboratory animals. Further, the National Institutes of Health established in 1962 an Animal Resources Branch in its Division of Research Facilities and Resources to serve as a focal point for identifying and meeting these problems in other installations. This Branch administers research grants directed at such problems as improving animal care techniques, diseases of laboratory animals, and improved diagnostic services for detecting diseases of laboratory animals. The Branch also serves as a center of information for laboratory animal use and gives technical assistance to grantees in the organization of laboratory animal programs and in the design of facilities. The staff of the Branch participates in the review of applications and plans submitted to the NIH for the construction of research animal buildings under the Health Research Facilities program. In fiscal year 1965, about $4.5 million was awarded on a 50-50 matching basis for the construction of new animal research units at medical schools and other research institutions. I might point out that some of the research activities supported by this Branch also benefit other domestic animals through better understanding of animal diseases and of their diagnosis and treatment.

The Public Health Service also cooperated with the Animal Care Panel, a nonfederal group of persons professionally interested in laboratory animal care, in the development of "A Guide for Laboratory Animal Facilities and Care," which

contains meaningful guidelines for the care of laboratory animals. This Guide was recently revised under the auspices of the Institute of Laboratory Animal Resources of the National Academy of Sciences - National Research Council. It is currently sent to each recipient of an NIH research grant and is also incorporated into the daily practice of animal units within the Public Health Service. The Guide covers the qualifications of personnel, materials and design for facilities, biological safety, and animal care procedure. I would like to include a copy of this excellent guide for the record.

In addition to being officially distributed by the Public Health Service, the "Guide for Laboratory Animal Facilities and Care" is also used by the newly established American Association for Accreditation of Laboratory Animal Care in the new program of voluntary accreditation of laboratory animal care facilities. Among the sponsors of this program are the American College of Physicians, the American Hospital Association, the American Heart Association, the American Medical Association, the Pharmaceutical Manufacturers Association, and the American Veterinary Medical Association. The program, which is similar in nature to the hospital accreditation program of the Joint Commission on Hospital Accreditation, is the outgrowth of earlier activities by the Animal Care Panel and the feasibility of the concept was tested during 1964.

The Animal Care Panel also conducts, through its local branches, a nationwide program of Laboratory Animal Technician Training and Certification. This program was launched in recognition of the importance of well trained animal handlers in the provision of quality laboratory animal care. Two of the institutes

of the National Institutes of Health have also supported specific research-oriented training programs in laboratory animal medicine. These programs have provided postdoctoral research training for a limited number of laboratory animal specialists.

I have described these activities of the Public Health Service and interested nonfederal organizations to emphasize that our concern with the problems being considered today has been translated into specific constructive programs. Since animals are so important in accomplishing our essential health mission and since the Public Health Service has a real commitment to humane treatment of these animals, we have a strong interest in maintaining a satisfactory approach to the problem of trying to assure that laboratory animals are well treated. This problem is far from simple. It involves difficult questions of definition as well as conflicting interpretations based on differences of emphasis. The complexities of the task should make us wary of simple solutions.

We can all agree on the need to handle laboratory animals humanely and to assure them proper housing, feed, and water. We can also agree that animals should be spared unnecessary pain and discomfort. We would stress, however, the imperative need to use animals in advancing medical research and the importance of considering the treatment of animals in the context of the research purpose. The value of animal research in reducing human suffering should not be neglected. The net benefit of any control of animal experimentation can only be validly assessed if the assessment includes an examination of the consequences of the control procedure on the effectiveness of medical research

of importance. We must recognize the danger of impeding the development of imaginative and productive research approaches through the imposition of rigidities in research methods and design or the substitution of less informed judgment for a judgment arrived at in conjunction with the trained investigator. What may be deemed to be unnecessary duplication from one point of view may be vital confirmation from the other. Without the blessing of hindsight, these judgments are frequently difficult to make in a definitive manner.

The careful design of a research project, including the determination of the need for the use of certain types and numbers of animals and the selection of specific experimental procedures is a central concern of the medical scientist and of his peers when they judge the quality of his work. Project design is never a casual or careless undertaking, and the decisions are the result of deliberate consideration and judgment by the researcher; but I would emphasize that changes in design and execution are characteristic of the dynamic development of a program in the doing.

The review process used by the Public Health Service in determining the scientific merit of a research grant application gives careful attention to the necessity for the project and the soundness of its basic design. This determination is made by groups of outstanding experts in the particular field of research and deals with the general strategy proposed by the scientist with realization that within such a strategic approach there is broad leeway for tactical modification as new knowledge unfolds. The soundness of this review process has often been acclaimed by groups appointed to study its effectiveness, most recently by the Wooldridge Committee which submitted its report to the President in January.

We submit that the history of research justifies a cautious attitude in the development of rules and regulations which operate to interfere with the judgment of a responsible medical scientist, for the primary attribute of his creative accomplishment is his ability to perceive when others cannot. We believe the necessary climate for productive research into the cause, prevention, and cure of disease must be preserved if the further solution of disease problems is to be anticipated with confidence by the American people.

We also feel that any steps taken in this area should be consistent with many local and State provisions. We should make sure that assumption of responsibility at the Federal level does not discourage initiative and responsibility at the institutional level where truly constructive maintenance of high standards must take place. We also believe that nonfederal efforts in the field of accreditation of laboratory animal care deserve to be encouraged and strengthened. An expression of Federal interest in this area ought to be compatible with these nonfederal activities.

In conclusion, we would like to reiterate our whole-hearted agreement with positive steps for the improvement and maintenance of high standards of care and treatment for animals used in the research effort against disease. The position of the Public Health Service on humane treatment of laboratory animals is clearly stated in the manual on research grants administration which is the operating guide on PHS research grants. We have given very careful consideration to the problems in this area for a number of years. Some new proposals have been introduced in this Congress. The Public Health Service and the Department of Health, Education, and Welfare are carefully studying these proposals because we

have some doubts about their effects on the productivity of research in the sciences related to health. We are also following closely the development of nonfederal accreditation mechanisms which have just recently become operative. The study which we have undertaken includes an assessment of the real needs in the laboratory animal field and whether new legislation is needed and, if so, what type of legislation. We will be in a position to present our conclusions from this study to the Committee during the next session of Congress. This Department, therefore, recommends that you defer action on the pending legislation at this time.

Thank you for this opportunity to speak to you about these difficult problems.

TAB 58

SOME GENERAL COMMENTS ON PHARMACOLOGY

JAMES A. SHANNON, M.D.

Director, National Institutes of Health
Bethesda, Maryland

Adapted from the after-dinner speech given at the 1965 Fall Meeting

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SOME GENERAL COMMENTS ON PHARMACOLOGY

James A. Shannon, M.D.
Director, National Institutes of Health
Bethesda, Maryland

(Adapted from the after-dinner speech given at the 1965 Fall Meeting)

The occasion of the 1965 Fall Meeting of the American Society for Pharmacology and Experimental Therapeutics provided an opportunity to share with its members some thoughts regarding pharmacology that have engaged my attention during the past three to four years.

This summary is intended to convey the salient features of my remarks. No attempt has been made to recapture the exact words used in Philadelphia. My remarks on that occasion were developed from rough notes.

The basic concept presented was that the primary objective of the National Institutes of Health is social in nature, namely, the improvement of the health of the American people. The achievement of this objective requires, among other things, the development of new knowledge of both a fundamental and applied nature and its distribution in usable form to a diverse group of users. Our deep involvement with science departments in academic institutions is a reflection of the fact that these environments represent the primary resource for the development of new knowledge. As a consequence, the NIH has a major concern for the provision of research support for individual scientists and groups of scientists, for the improvement of career opportunities in biomedical research,and for the development of future generations of investigators and teachers. It also has concern for the provision of adequate physical resources and for the health and vigor of the institutions which serve as the setting for the overall scientific enterprise. Important as they are, these activities are derived scientific missions; the primary one remains the improvement of the health of the American people. I would emphasize that my remarks concerning pharmacology are meaningful only in this context.

The field of pharmacology was assessed, neither as a didactic course in the preclinical phase of medical education, nor as an aggregate of departments in which a variety of research programs are conducted, but rather as a subject area to which a number of scientific disciplines can contribute in a uniquely effective way to the solution of serious medical problems. The viewpoint expressed in Philadelphia was that of a science administrator charged with the responsibility of utilizing the most effective means by which public funds can be expended in such an effort. This viewpoint is different, necessarily, from the viewpoint of the individual scientist.

My thesis was--and remains--a simple one. I am convinced that the main thrust of American pharmacology is too narrowly focused. For example, particular emphasis is being placed on detailed studies of basic phenomena that are the common concern of the biochemist and that new breed of biologist who addresses himself to the understanding of phenomena on a subsystem, cellular, and molecular level. One cannot or should not complain about such activities on the part of the individual scientist, and that certainly is not my purpose. However, when the professionals of a field as a whole do not engage themselves with a number of the pressing problems they are peculiarly and appropriately suited to solve, then those who are concerned with an assessment of the national effort must question the reasonableness of the overall program emphasis. An overview of the effort in those scientific fields which traditionally have been the concern of the professionals in pharmacology gives little comfort when viewed in this light. One finds, for example, that new drug development has been relegated more or less exclusively to the pharmaceutical industry. The clinical evaluation of drugs has been largely left to clinicians, many with little experience in the broader aspects of pharmacology. Toxicology has been too frequently dismissed as a dreary wasteland of routine drudgery. And finally, the consequences of an increasingly hostile chemical environment are generally believed to be the problem of others.

It is my belief that American pharmacology has not responded adequately to the challenges presented by the increasingly complex chemical milieu of modern society. If it is to do so, it must extend its interests to give serious attention to a number of areas currently neglected.

The pharmacology "establishment," if there be such a thing, cannot limit its studies of drugs to isolated systems, concentrating on an examination of detailed biological activity in well defined, quantifiable systems. Nor can it limit itself to studies that assess the relative activity of a series of compounds on simple biological systems without regard to the organism as a whole or the purposeful use of specific compounds.

Adequate attention is not given to the hazards associated with new and potent drugs, nor for that matter, old drugs useful in the prevention and treatment of health problems. Particular difficulties arise in chronic illnesses which require that agents be administered over very long periods. Long-term toxic reactions of such simple compounds as aspirin or such complex substances as steroids are too frequently discovered by accident rather than as the result of planned study of the long-term consequences of such medication. The effects of thalidomide on the foetus during the early months of pregnancy produced a flurry of newly oriented pharmacological activity long since subsided. There is little input aimed at a clarification of the underlying effects of antifertility agents in the human, leaving to the clinician the assessment of toxic hazards through clinical observation of end effects. There has been inadequate pharmacological involvement in defining the toxicological hazard of such drugs as the anticoagulants, the diuretic, the antidiabetic, and antihypertensive agents utilized very widely for maintenance therapy. An even more difficult problem is that of determining or predicting the harmful effects of combined drug therapy, including those associated with intermittent drug administration superimposed upon continuous treatment with, or exposure to, other agents.

In another health problem that could logically be the concern of the pharmacologist are the many diseases involving protozoan or more complex parasitism, such as bilharziasis, filariasis, drug resistant forms of malaria, and others. These diseases are still devastating vast regions of the world, and some are of immediate or potential significance to this country. There is a need to define the critical susceptibility of these organisms to various agents, looking to the rational development of better therapeutic agents. The experience with malaria dating from World War II is a case in point. The more effective antimalarials then developed appeared to be very nearly ideal. This is true no longer. Were the biology of the parasite better understood, it seems likely that more effective drugs could be developed. Who is better prepared than the pharmacologist, committed as he is to the study of the interaction of chemicals with biological systems, to undertake the definition of susceptible targets in such a complex organism as a protozoan with the aim of a rational approach to drug development?

It should be obvious from these as well as other examples that could be cited that the pharmacologist has a major and challenging role to play in the development of new therapeutic agents. Drug development can no longer be equated by the pharmacologist with the routine screening of chemical agents in conventional biological systems. To play the larger role envisaged, the pharmacologist's sights must be raised and the capabilities of the departments within which his work is performed considerably broadened in their scientific content.

Finally, little attention is given by the academic world to an area of peculiar concern to the pharmacologist. This relates to the systematic development of information upon which generalizations can be developed that would be useful for the rational development of therapeutic agents. This subject was covered rather explicitly by Drs. Brodie, Rall, and Cosmides in a general article in Science some months ago (June 18, 1965, Vol. 148, No. 3677, pages 1547-1554).

Moving from the potential role of the pharmacologist in the development of therapeutic agents, the point was made that pharmacologists can no longer neglect the exploration of very practical problems derived from our increasingly hostile environment.

Increasingly our environment is subjected to the massive and often indiscriminate introduction of chemical agents. These include food additives, industrial and agricultural chemicals, and air and water pollutants. As with drugs used in therapy, these agents may produce serious chronic as well as acute harmful effects. Nevertheless, they are generally regarded by pharmacologists as being outside the mainstream of their interest. As a result, those studies that are being conducted are too frequently supervised by individuals with no, or inadequate, formal training in pharmacology. Yet, from the viewpoint of their impact upon society, environmental hazards may well constitute the most critically needed areas for intensive and sophisticated pharmacologic study.

These are some examples of problems that should be (but are insufficiently) engaging the energies of American pharmacologists. It has been our experience that most pharmacologists have little awareness of the potentially great social significance that could result from their activities. They function chiefly in rather narrow discipline-oriented groups instead of broad mission-oriented groups. As a consequence, there is little opportunity for the generation of illuminating observations and for the subsequent development of unifying generalizations with socially consequential results.

It is, I believe, unrealistic to expect substantially increased support from either the public or private sector for the pursuit of science primarily for the sake of science when at the same time, engagement with major social issues is avoided. Science gains by having a clear understanding of its actual or potential relationship to social problems and goals. If pharmacology is to become more vital, it must find ways to develop a clearer and broader understanding of its potential contributions to the major health problems of our time.

When science is not responsive to society's needs under existing institutional forms, new forms must necessarily be created. As a consequence of considerations such as have been detailed, the NIH is in the process of developing

more broadly conceived programs in pharmacology and toxicology with the aim of stimulating greater efforts in many neglected areas. Our Society insists upon no less of an effort on the part of an organization so deeply committed to the health of the public.

In closing, I wish to reemphasize that my remarks are directed to the "pharmacological establishment" in general and are not meant to be critical of the activities of individual scientists in the field. I would hope that the members of the Society would give these comments their serious consideration. My thanks to the Society for providing me with the opportunity to present these thoughts, and I would welcome your reactions and comments to these ideas.

TAB 59

VIEWPOINT

An Interview with James A. Shannon, M.D., PH.D.

The director of the National Institutes of Health, Dr. James A. Shannon, is regarded as one of the nation's leading influences on the development of biomedical research. The 61-year-old native of Hollis, N.Y., has been director of NIH for a decade, with the responsibility for helping to formulate broad national research policies. NIH itself supports intramural and extramural research and allied activities on a billion-dollar annual budget, about 40% of the nation's medical research support. Dr. Shannon received an M.D. degree in 1929 and a Ph.D. in physiology in 1935 from New York University. Renal physiology and diabetes were among his research interests. In World War II, he played a leading role in malaria research. He became associate director of the National Heart Institute in 1949, associate NIH director in 1952, and director in 1955.

Coordinated effort needed in gerontology

Q. Are you satisfied with progress in gerontology?

DR. SHANNON: No. We need programs in universities that are multidisciplinary but committed as a group to provide the "critical mass" of coordinated effort necessary to make progress. We also need to provide opportunities for training in research. Dr. Nathan Shock's gerontology unit in Baltimore is demonstrating that research in gerontology can be done on a multidisciplinary and long-term basis. This is a direct NIH operation. A building is to be constructed, and Johns Hopkins, the University of Maryland, and state agencies will be able to do gerontological work under one roof with

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VIEWPOINT

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Dr. Shock's group. However, I must point out—as I have to Congress—that we do not yet have an extramural program of national dimensions. Clearly, we have been unable to convince the scientific community at large of the net worth of serious study in this field.

Q. *What needs to be done?*

DR. SHANNON: We need a type of administrative vehicle that provides a focal point for broad investigations and the training of scientists.

Q. *The administration sought authority in Congress this year for building certain kinds of health research facilities, or institutes, at universities. Federal grants were to cover all construction costs. I recall that gerontology was mentioned as a field for which this authority would be used. Is this the vehicle you mean?*

DR. SHANNON: Yes. We wanted this authority for gerontology, pharmacology, toxicology, dental sciences, and other fields that should be expanded. A main bottleneck has been the lack of the physical means to do complex research in key fields. We thought of these institutes as bringing various investigators together for operations beyond the usual departmental structure of individual institutions. The institutes would focus the efforts of investigators in one structure and provide an identification that is lacking when research on aging is spread through various departments. This request for broad construction au-

(Continued on page 73A)

VIEWPOINT

(Continued from page 68A)

thority was turned down in the House. Perhaps a request for authority in specific fields may be received favorably in the future.

Q. *NIH has supported regional centers in aging. I gather these did not house all their activities under one roof.*

DR. SHANNON: This makes it difficult to organize interdisciplinary activities. The proposed institute approach would enable setting up a core program in research on aging that would attract graduate students. We envision 4 or 6 institutes of aging dealing with laboratory, clinical, and field studies in behavioral and biologic aspects.

Q. *What main problems should be tackled?*

DR. SHANNON: There are two main, intermingled problems, as I see the situation. First, we must use medical science to investigate the behavioral and biologic problems of aging. Second, we need to investigate the socioeconomic environment of old people to see what factors in-

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VIEWPOINT

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fluence their well-being. For instance, retirement communities in the South and Southwest are being set up by commercial enterprises without a built-in attempt to find out whether the intended social climate is suitable and the needs of the elderly will be satisfied.

I hope the coming decade will see experimentation in different types of environments. We should have a sound basis for making suggestions about the social requirements of the aging. To ignore their needs in the communities where they spend much of their lives and to think only of retirement communities in mild climates are not solutions.

Q. There has been some feeling in gerontological quarters that NIH should take greater leadership responsibilities for the field. As I understand the criticism, NIH is not doing enough to encourage investigators to enter gerontology.

DR. SHANNON: This is a complicated area. Our job is to make the means available for qualified investigators to undertake worthy research. Nobody, I hope, wants NIH to lead investigators by the hand into certain fields. Nobody, I hope, wants a federal prescription of research undertakings. I can only say that if investigators and institutions are uninterested in gerontology, there is little we can do. NIH can only go so far as Congress and the scientific community permit.

TAB 60

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MEDICAL RESEARCH

JAMES A. SHANNON[1]

(Received for publication June 3, 1965)

It is gratifying to address an organization that has been so long in the forefront of medical service and research, and one that has proved so adaptable to revolutionary changes wrought by science. For such changes are in progress today with increasing momentum. They are felt in the institutions of higher learning, in the clinic, in the physician's office, and in the community at large. I have no doubt that the National Tuberculosis Association will play an active part in these changes with traditional spirit and competence.

One can say this with assurance, in reflecting on the history of the contributions of the National Tuberculosis Association to tuberculosis control in this country. These relate to a comprehension of social components of disease and to the effective use of health education, mass screening, and the health survey. The National Tuberculosis Association has played an equally important role in the dissemination of information to physicians, the development of rehabilitation, and the successful application of chemotherapy. Finally—though one speaks with considerably less enthusiasm—there has been the sad but important lesson learned from relaxing too soon.

[1] From the National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

In the history of tuberculosis control, the leadership of the National Tuberculosis Association is clearly apparent. Recently, that superb leadership has been extended to the control of other respiratory diseases. The strategy and tactics of this effort will doubtless be determined, in part, by some of the forces and trends we will be discussing this evening.

The Postwar Development of Medical Science

It is clear that, since World War II, the world has entered a period in which science and technology have a position of unprecedented importance, and we observe that knowledge begets knowledge at an accelerating rate. Much, if not most, science and technology is applied to the control of our environment or our reactions to it. The effort to "subdue the earth"—to gain control over the physical and biologic events that condition and shape our lives—is as old as mankind, but modern science has proved the superlative instrument. Most important in man's relation to his environment is his state of health, and scientists from all fields are applying themselves to health-related phenomena in increasing numbers.

A quantitative measure of this trend is the change in the proportion of all research and

development that is devoted to medical research. Since the mid-century point, expenditures for medical research have risen in the United States from about 5.6 per cent to 8.8 per cent of all Research and Development. In absolute terms, the growth has been even more impressive: from about $160 million in 1950 to an estimated $1.85 billion in 1965. This represents an escalation of effort to improve the human condition, drawing on all sectors of the economy—government, industry, and philanthropy. And it will continue to affect higher education and medical service in major ways.

The Scientific Base of Medical Education

Medical education in the United States is undergoing a major transition. One obvious change is expansion, in the form of new schools, medical centers, laboratories, and enlarged student capacity. Between 1957 and 1963, the total operating expenses of medical schools more than doubled, rising from $240 million to an estimated $600 million.[2] The number of full-time faculty has more than tripled since 1951: 4,000 to 14,500. Over the same period, the student body has risen from about 26,000 to 32,000. The total student load for all schools last year was 70,000, counting interns and residents, graduate students and postdoctoral fellows in the sciences, and students in the other health professions.

Equally significant changes concern the framework and content of education. There has been an accumulation of knowledge in old disciplines through the entry of mathematics and the physical sciences; the behavioral sciences have come of age; and medical research tends to cross disciplinary lines rather than be restrained within them. These developments could lead to curriculum changes at the very least, and even to modification of the departmental structure of the medical schools.

Broadly speaking, the medical sciences have emerged in a central role in the educational environment. This represents a flowering of programs that date back in some schools to the turn of the century, when a scientific base for medical education was exceptional. Yet men of vision, like Abraham Flexner, stressed the essentiality of research in the educational process.

Flexner's report to the Carnegie Foundation in 1910—a study that revolutionized medical education in this country—described three stages in the evolution of medical teaching. The first and longest was the era of *dogma*. The teachings of Hippocrates and Galen, though derived largely from observation and experience, were transmitted for centuries as an authoritative canon. Flexner calls the second era *empiric*. It began with the introduction of anatomy in the sixteenth century and reached its zenith in the eighteenth. This was a period of heroic therapeutic measures, sometimes deduced from metaphysical assumptions, but increasingly derived from observation and experiment. Teaching during this period was based as much on persuasion as on rigorous proof. In the third era, medicine is conceived to be *grounded in modern science*.

Some distinguishing characteristics of scientific medicine, according to Flexner, are these: procedures, instruments, and drugs are constantly subjected to critical evaluation; speculation is minimized except as a basis for further study; and progress is made through research, i.e., accumulation of facts and their analysis. Furthermore, the progress of science and the intelligent practice of medicine employ the same technique: observation, hypothesis (or diagnosis), action, critical review of progress, and perhaps modification. Flexner states: "The student must be trained to the positive exercise of his faculties; and if so trained, the medical school begins rather than completes his medical education."

The Physician in an Era of Science

The accelerating emergence of knowledge not only implies that the physician must be scientifically oriented, but that a means must be purposely built into the educational system for his continuing self-development. Today's graduate, given an average life span, will be practicing medicine into the next century. In this era of science and technology, he will feel keenly his "obligation to know." Almost surely, he will seek formalized opportunities for continuing education beyond the short-term graduate course.

Without being too specific, one can confidently predict that the dynamic state of knowledge and its demands upon physicians will occasion other significant trends. Changes may be expected in premedical education, in the preparation for

[2] Includes teaching expenses of university hospitals.

clinical medicine, and perhaps in licensure procedures. The ground swell of science will be felt in all aspects of medical education and service.

The new dynamic state of medical science is leading to profound changes in medical care. The growing complexity of knowledge, techniques, equipment, and so forth, has been a prime mover in the trend toward specialization and group practice. In short, more specialized knowledge has led to more specialization in virtually every branch of medicine. A parallel development has been the expansion of services to physicians, ranging from business and clerical assistance to professional laboratory and clinical procedures. Other sweeping changes are seen in the economics of medical care as a result of expanding health insurance coverage, institutional medicine, and governmental insurance and support programs. Whatever our personal views on these trends, we must recognize that they are a product of complex interactions between socioeconomic factors and the "state of the art." As trends, they will continue, and will lead us far from the older type of personalized medical are.

The Regional Medical Complex

The over-all picture is one of transition in the ways that medical services are deployed. In some areas of medicine, mission-oriented programs, as well as specialized knowledge and facilities, may combine to produce specialized institutions deployed on a regional rather than on a community level. Such major health problems as cancer, heart disease, and stroke are amenable to an approach in which these concepts are combined, less as separable entities than as part of a complicated research, educational, service complex.

Such a regional medical center—say, a university hospital or other source of knowledge, skill, and equipment—must be characterized by broad scientific excellence, extensive teaching capability, and adequate means for specialized study, diagnosis, and treatment of an array of important diseases. Such a center cannot be sustained on a community basis. But medical care of the quality found in our best centers can reach the population at large through related local facilities.

The concept of a regional network is emerging for several reasons. One, it is a natural outgrowth of specialization and the growing complexity of diagnostic and therapeutic procedures in many fields. More important, it removes a major limitation on the continued outflow of information useful to the physician in the community as he approaches his daily, increasingly complex, professional problems.

The evolution of the regional medical complex cannot proceed apace without the cooperation and active support of the medical profession, the public, and the agencies that see it as a means of furthering their missions. Voluntary health agencies, Federal research programs, and state and local health departments could lend valuable help. A network of case-finding and treatment centers, community-based and strongly linked to sources of medical knowledge, could characterize a new era in disease control.

Setting the Standard of Medical Service

The college-affiliated hospital or medical center, academically staffed and research-oriented, is setting the standard for medical care in this country. It is the environment from which today's medical graduate emerges, the environment he will demand for his patients and his own self-development. And the community center with equivalent standards, multiplied many times around the hub of a great medical school complex, is a natural extension. Already one feels a strong and growing community demand for medical service of the caliber found in the Nation's centers of excellence.

Schools, professional associations, supportive agencies, and community services have their parts to play in extending the research base of medical education and in bringing scientific medicine to the greatest possible number of people. The physician, with the aid of these groups, will seek better means to further his self-development, adapting and contributing to the dynamic state of knowledge. And the voluntary health agency will remain an integral part of the medical community, continuing to serve importantly in the conquest of disease.

TAB 61

THE NATIONAL PURPOSE IN SUPPORT OF HEALTH RESEARCH*

> He who has health has hope, and he who has hope has everything.
>
> --Arabian proverb

The relevance of health to our national purpose has been expressed recently by President Johnson: "The health of our people is inescapably the foundation for fulfillment of all our aspirations." Through increasing levels of support, Congress has repeatedly demonstrated that research is indeed an instrument of national policy--not only health research, but also the broad spectrum of basic science of which it is a part.

Today, as never before, there is widespread recognition of the contribution of science to our life as a nation. As the President has observed, no national policy or purpose of the United States is unaffected by the present state or prospective scope of our scientific knowledge. In an age that urges full utilization of men and ideas, there is no doubt about the soundness, firmness or conviction of this commitment. Yet, as is true of any pursuit, we

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*Presented for Dr. James A. Shannon, Director, NIH, before the National Conference on Dental Research and Education, Washington, D.C., October 4, 1965, by Dr. Stuart M. Sessoms, Deputy Director, NIH.

must periodically examine this posture to assure that it is in proper balance with the total national interest. And certainly, the relationship between education and research--the concern of this conference--is a critical one.

I am realist enough to recognize that research, an essential ingredient of education, must serve education, not compete with it. And I am optimist enough to believe that a way can be found to achieve superiority and unity in both. For the strength of nations today is measured by their intellectual capacity. The atomic bomb and then Sputnik displaced the previous emphasis on military and technical prowess and symbolized a new era in which intellectual capacity would be the definitive measure of a nation's strength.

Thus, we are addressing ourselves to an issue which, in its broader terms, strikes at the very heart of our national welfare and security. It is a great honor for me to contribute to one aspect of this vital dialogue.

The National Commitment to Medical Research

The present Federal involvement in science represents the culmination of a series of crises in our Nation's history, each of which resulted in a deepening commitment to the support of biomedical research. The needs of the Civil War, for example, gave rise to an

expanded Army medical department, with a research facility supported by a library that has since developed into the National Library of Medicine. Another lasting result of that war was the formation of the National Academy of Sciences. The Academy, in turn, created the National Research Council in 1917 to help Federal agencies beset by problems of World War I. In World War II the Office of Scientific Research and Development mobilized science on a larger scale. And as an outgrowth of the events of that war, the National Science Foundation was established in 1950, dedicated to the development of science in peacetime.

Other emergencies similarly left their mark. The threat of grave epidemics during the great period of immigration in the 1880's resulted in the establishment of the Hygienic Laboratory at the port of New York. This installation of the Public Health Service was the forebear of the National Institutes of Health.

The general pattern, however, was to mount a program for meeting the current exigency and then to curtail or abandon it when the problem ebbed. It was not until World War II that we came to terms with our research position and the need for an orderly pursuit of new knowledge.

This crisis caught us weak in basic science and dependent on Europe for fundamental knowledge necessary to the development of new weapons, both military and biomedical. Arguing that "basic research is the pacemaker of technological progress," Dr. Vannevar Bush recommended to President Roosevelt that Federal funds be directed to the advancement of fundamental science. The American people, too, having benefited greatly from the by-products of war-time research, were more responsive to the need for continued research support. Thus, the stage was set for the forging of a major and lasting commitment between the Federal Government and the scientific community.

Some measure of this commitment can be gained by contrasting the flourishing research of today with that before the war. Four decades ago, the total research expenditure of the Public Health Service was less than half a million dollars. Research funds for fiscal 1965 totalled about $800 million. This was largely awarded, of course, in grants and contracts to private, nonprofit institutions.

A look back to the turn of the century, when research was privately supported for the most part, shows even more compellingly the distance travelled. The Rockefeller Institute for Medical Research determined to make "knowledge relating to various subjects

available for the protection of the health of the public." A scientific journal was founded. But it soon suffered from a scarcity of publishable material due to a lack of good research in the institutions of the country. This pointed to the need for high-quality studies, and led to the Institute's program of research grants.

The National Cancer Institute, authorized by the Congress within the Public Health Service in 1937, was the first of nine National Institutes of Health. These arose in response to another national crisis--the mounting toll of chronic disease. The Institutes had permanent authority to make Federal grants for medical research in non-Federal organizations. Research support, however, remained at a modest level until the end of the war.

Advancing the State of the Art

Prior to that time, the capabilities were lacking for a large-scale effort against mounting health problems. It remained for the war-born, basic-science contributions to advance dramatically the "state of the art." This represents a broad, indeterminate base that cannot be controlled in mission-oriented activities, and yet has developed rapidly in recent years.

One might ask, by way of illustration, if the state of the biomedical art in 1918 was such that, given any sum of money, the problem of poliomyelitis could have been broken at that time. Or, with any amount of funding and any amount of effort, would it have been possible to develop in the '20's or '30's what we know today to be heart surgery? In both cases I believe the answer is no, considering the absence of the necessary basic knowledge. The art at that time--the broad base of knowledge--was grossly inadequate to permit solutions to those very practical problems. Today, however, we can speak of accelerating the advancement of the biomedical art, through support of science on a very broad front.

Dental Research

It is also possible that progress against the long-neglected problems of oral health would have lagged awhile if the national decision to do something about them had come much earlier. As it was, when the National Institute of Dental Research was established in 1948, the time was ripe for identifying, expanding and advancing the scientific base relevant to dental disease. With respect to dentistry, this became our national purpose.

Practice in dentistry had proceeded out of engineering and mechanical types of development, with no real engagement of the underlying phenomena that bear on problems of dental health.

Through an increasing involvement of the basic sciences, the Institute has, within the space of a few years, contributed greatly to a new understanding of dental problems which holds promise for their ultimate prevention.

Moreover, this broad-gauged dental research has contributed new knowledge and methodology to the field of medicine as a whole. For example, work on the effect of fluoride ions in stabilizing tooth enamel has implications for the bone in osteoporosis. Similarly, epidemiologic studies of the dental status of various populations have led to even broader inquiries into the genetics involved. And germ-free technology has been enlarged and expanded following its demonstrated value in research on caries and periodontal disease. Nor does this exhaust all the cross-fertilization that the Dental Institute has inspired.

Having fruitfully demonstrated and extended the biomedical base of dental research, we are now attempting to replicate the Dental Institute in selected university settings. While moving toward the establishment of these multidisciplinary centers, we are encouraging research in nondental as well as dental environments. Recently, for example, a leading engineering school, aided by the Dental Institute, has elected to commit a major research effort to the development of better dental and medical materials.

Research Outlook

In carrying out this broad commitment to health research, we must, as a practical measure, consider if and where there may be a point of diminishing returns. Is there a point in the support of science, particularly biomedical science, beyond which the returns necessarily diminish sharply as a result of intrinsic limitations or immutable conditions, social, economic or technological? In short, will we be limited by the state of the art?

It is my conviction that the biological sciences are less limited today than ever before because science and technology in general are being supported on such a broad front. In fact, the biosciences have benefited tremendously by the prior emphasis in the '30's and '40's on chemistry, and in the '40's and '50's on physics. We are now recipients of the benefits of a $21 billion research and development program--benefits that have scarcely been put to use in the fields of biology and medicine.

The problem here is not a lack of research opportunity, but a lack of scientific resources, particularly trained manpower. What is faced now is the need to select goals quite broadly, and these may be goals of the most fundamental research. I would venture to say that science in the '60's and '70's will be progressively dominated by the problems and goals which conventionally come into the biological frame of reference.

Education's Research Base

If it is our national purpose to develop intellectual capability applicable to health and welfare, we must concern ourselves boldly with the quality of education in medicine and related fields. This implies further intensive development of education's research base.

The Federal Government today underwrites about 65 percent of the medical research and an even higher proportion of the dental research in this country. Educational institutions receive nearly half of each Federal dollar spent on medical science, but only 12 cents of the Federal dollar spent for all R & D. Thus, Federal agencies concerned with medical and other health-related research are far more involved with the schools in the accomplishment of their missions than are other Federal agencies with science interests.

NIH is the major Federal supporter of science in colleges and universities. Some impression of the distribution of NIH activities, with their implications for support of education's research base, may be gained from analysis of the consolidated appropriations for 1966. Out of a total appropriation of about $1.2 billion, 9 percent will go for matching construction grants, 22 percent for training awards, 50 percent for research grants, 15 percent for collaborative studies and direct research at Bethesda, and finally, 4 percent for other operations such as biologics control and technical assistance to the

States. Thus, about a third of NIH funds will be spent for the development of scientific resources (facilities, equipment, manpower) and the remaining two thirds for current research.

What has been the overall effect of NIH support? Recently I was quoted as saying that 90 percent of the discoveries in medical research over the past ten years owe something to NIH, and that this support has brought medical knowledge to a point it would not otherwise have reached until 1975.

Seeing these words in print, I wondered whether my statement might seem prideful to some. I hope not. In fact, when we consider that 40 percent of the Nation's medical research support comes from NIH programs, it seems reasonable to claim for NIH a substantial participation in the dramatic progress that has been made against certain forms of heart disease, cancer, mental illness, and other major health problems.

Within the schools and their affiliated hospitals, basic and clinical science programs have been strengthened. The environment for training physicians, dentists, and biomedical investigators has been enriched, directly through training grants and fellowships and indirectly through support of research projects.

NIH research grants to educational institutions have increased 15-fold since 1955--from $27 million to $400 million. There has been an ever-widening participation, with nearly 400 institutions now receiving some aid. These trends have resulted in a broadening of the base of excellence. In 1948 the top 25 universities received 50 percent of NIH funds; in 1963, only 42 percent. Moreover, all parts of the universities have been affected--graduate, professional, agricultural, veterinary, and even undergraduate colleges of arts and sciences.

Another major effect is beginning to be felt. This is an impact on the character and quality of medical and dental service, brought about through new knowledge and public demand. As knowledge is developed and tested in centers of excellence across the land--as investigators and specialists apply their knowledge and skills to increasing numbers of patients--the health professions at large and the general public want to see the benefits of research made available to all the people. Thus, a pressure is building to extend the quality of clinical investigation from the great university centers into medical facilities and practice at the community level.

Needs for the Future

These influences, in turn, cannot help but shape our national purpose and guide the direction of its ultimate aim: the betterment of the human condition. They call for a new orientation and place new responsibility on the Government and the university, the public and private sectors alike. While maintaining the momentum of our research effort, we must move vigorously toward enlarging and improving opportunities for teaching and application. Such positive moves will also serve to redress imbalances that may exist among the university functions of education, research and service.

More specifically:

. . . Greater efforts should be made to provide sound undergraduate experience based on science.

. . . The schools should be able to provide research training in depth, or at least exposure in depth, with a view to orienting the student to the dynamic nature of education and future practice in an age of rapid scientific advancement.

. . . Better mechanisms must be found for helping schools to augment and sustain educational programs grounded in scientific investigation.

. . . Finally, adequate provision must be made for continuous education of the professional. For the dental as well as the

medical practitioner, such a program might be based in community facilities connected with a university center.

An invaluable channel for the continuous outflow of information to the health professions will be opened by the regional medical complexes recently authorized by the Congress. Established to bring to patients--particularly those afflicted with heart disease, cancer or stroke--the latest advances in the diagnosis and treatment of major disorders, these regional cooperative arrangements will reflect the latest approaches to research, education, training and demonstrations of patient care.

By participating in the work of these centers, the university will have a greater opportunity to fulfill responsibilities in both the education and service areas.

In dentistry, it is of some historical interest to note a milestone of development, when the Kellogg Foundation as long ago as 1939 provided substantial dollar support for the construction and operation of an Institute of Graduate and Postgraduate Dentistry at the University of Michigan. This center, through the years, has served the continuing educational needs of dentists the world over. But much more must be done, and we may hope, will be done.

There is need for more vigorous and imaginative efforts to attract young people into the ranks of biomedical manpower. It is

predicted that by 1975 there will be 25 new medical schools and 10 new dental schools to help meet anticipated peak demands. Training programs will have to be accelerated in this period of development. As a minimum, we need to assure a constant proportion of manpower flow into the biomedical areas to meet research, teaching and advanced clinical requirements.

Today, through the continuing contributions of basic science, we stand at the threshold of unprecedented biomedical advances. We are in position to deploy our resources against the chronic, degenerative diseases that are so costly in human and economic terms. We are committed to this purpose through a further build-up of our research base and the development of programs of education and demonstration to harness and apply new knowledge.

In this effort, we look to the continuing partnership of government and the university. Together they will develop the necessary knowledge and capability for tomorrow's great steps forward. We may well take new vision and challenge from Emerson's words:

> We think our civilization is near its meridian, but we are yet only at the cockcrowing and the morning star.

TAB 62

BIOMEDICAL SCIENCES--PRESENT STATUS AND PROBLEMS*

by James A. Shannon, M.D.**

The impact of growth of the biomedical sciences, particularly over the past decade, may necessitate major changes in institutional forms. A brief review of the development of these sciences will help explain the need and define the shape and direction of future programs.

In 1940 those portions of science relevant to the understanding of disease served as a base for the categorical structure of the National Institutes of Health. In the latter part of the forties and the early fifties, they further served as the base for support of a nationwide effort against all the major health problems. In the 1950's the thrust of the forties was to continue, but changes in the scientific base occurred. There began to emerge, in a highly purposeful way, an understanding of the molecular dynamics of biological phenomena, an application of physical sciences and mathematics as disciplines capable of far-reaching contributions, a shaping and refinement of behavioral studies to a point where the term "science" was now warranted, and a group of studies aimed at the broad problems of human development.

As we approach the sixties, there comes to attention a searching inquiry as to what was wrought in the past two decades. Where are we now and where are we going? This inquiry can be fruitful, but it should

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** Director, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

not only probe the present scene and assure its continuation in the future; it should also look quite freely for new devices, new mechanisms, and new basic activities that are more suited for the next twenty years than a simple persistence of the habits developed up to the present time.

Today the field of biomedical science is characterized largely by undifferentiated effort through the support of individual scientists. There is still a multiplicity of disease problems, very few of the major ones having been resolved over the past twenty years. Many scientists have withdrawn from the study of disease as such, and an understandable and valid concept of science for science's sake has emerged. But this is not healthy if it implies a retreat from problems that must be attacked for a variety of social reasons. And indeed, in addition to the spectrum of diseases that remain prevalent and devastating, we have identified new areas demanding attention. Consider, for example, the study of the biological, behavioral, and intellectual development of the child as an end in itself, with a view to coping ultimately with mental retardation and assuring healthy intellectual growth. Here, we are beginning to explore environmental factors with a wholly new social orientation.

Our national program in support of science is entering a phase in which the decision whether to support a given field depends less upon technical considerations than upon social need. If we are to continue to have adequate support for the fundamental as well as the applied (and for strictly applied research as opposed to developmental engineering),

then the aggregate effort must be to develop some sense of balance between the two approaches. Take, for example, the problem of water pollution, which has long since ceased to challenge the medical investigator. Water pollution, beyond a doubt, will yield to techniques of management--to an approach that relates the capacity of the nation's water resources to the ways in which we use them. The field of air pollution affords a comparable case. We certainly inhale numerous carcinogens in perhaps dangerous amounts, not only from cigarettes but from a wide variety of hydrocarbon wastes; but knowledge of these carcinogens does not provide the thrust for their elimination nearly so much as the social pressure of people living within our metropolitan areas who insist on clean air as essential for comfort. Or again, a modern agricultural industry has introduced into our daily diet an array of potent chemical agents, many of which have been inadequately assessed. Here, a sufficient public clamor could provide the impetus for corrective measures, including the necessary scientific investigation.

Such complex problems as these must be considered with a view to their orderly exploration. This exploration, at whatever level it is undertaken, does not always coincide with the neat departmental structure of our universities and professional schools. These organizations, developed first for undergraduate education and later modified to provide discipline-oriented training for the predoctoral student, more or less tend to perpetuate themselves in the image of their forebears. An

examination of our academic enterprise, whether cursory or in depth, reveals an absence of institutional design to provide meaningful acquisition or utilization of the far-ranging new knowledge that will be necessary to meet paramount social needs. This, indeed, posits a critical situation confronting the scientist on the one hand and the public administrator on the other.

Most federal agencies have social purposes. The defense department provides for the physical protection of our national security; the agriculture agency is responsible for a sound source of high-quality food and effective handling of a wider range of agricultural products, including fibers, woods, and the like; and the public health branch strives to ensure buoyant health, emotional stability, and optimal intellectual growth. Up to the present time, it has fortunately been possible, in accepting these social missions, to convince the Congress and through them the American people that the setting of priorities, the selection of fields, the development of terms and conditions of support must be left in the hands of scientists if the work is to be done on a productive level. The setting of social goals is probably not the scientist's role. If he chooses, however, to operate within a frame of reference that has certain goals, then he will surely be influenced by them.

Medicine must provide the biomedical sciences with institutional forms that permit the realistic isolation of reasonable technical and scientific objectives. It must support work toward those objectives in

a form flexible enough to contribute to the strength of independent imaginative activity while yielding practical scientific advances. Providing support for the independent scientist is a simple matter, and all of the agencies that have undertaken to do so over the past ten or twenty years have succeeded. But establishing a system of support that capitalizes on progress and directs itself to attainable goals is quite difficult. The biomedical scientist in general has the intellectual capability to produce needed and useful knowledge, but he usually does not have control of all the necessary resources. By contrast, the Federal administrator, exhorted by Congress to activate the array of scientific disciplines required to meet an objective, may find the individual scientist apathetic toward participating in a group effort that places little premium on either his capability or the goals he perceives as important. And yet, in the face of this conflict, society demands that biomedical enterprise in the aggregate be a socially purposeful one. That is the problem.

We are quite a long way toward the solution of that problem, acknowledging and sustaining, as in the past, the drive of the individual investigator for scientific progress and simultaneously providing an environment where his efforts, together with those of his related colleagues, can be more socially focused. This can be accomplished in a way that will tend to strengthen rather than weaken a somewhat changed university. The simplest solution may be to permit in selected areas

the progressive build-up of quasi-research institutes ("quasi" because I do not refer to free-standing research institutes, external to our universities) within the university system of graduate education. These would serve as resources for professional education without depending upon their contribution to it as the basis of support.

Such institutes are viewed by some with concern, by others as being the hopeful way to meet the social need for scientific advances. There is a fair amount of experimentation under way. The Division of Communication Sciences at the Massachusetts Institute of Technology would qualify, and the Institute of Human Genetics at the University of Michigan. There are also the older forms of cancer and cardiovascular institutes, some good, some poor--but the fact that some of these are poor does not necessarily mean they can never be good. Clearly, without some new institutional forms, information essential to the resolution of certain major problems would not be forthcoming, and we therefore have in the process of development a series of institutes motivated by specific, socially desirable biomedical goals. These should be able to build upon the experience of similar endeavors in the past. Institutes of this sort can be constructed and developed within the framework of the institution, and perhaps will fluorish to a far greater extent than would be possible with comfortable support distributed through the normal disciplines of the university.

The dental sciences provide a good example of a field that needs such attention. The social cost of dental disease is fantastic. There are 50 dental schools now, and it is calculated that in terms of reparative dentistry there should be 160. Since we are not going to have 160 dental schools, the only alternative is to determine the underlying causation of dental disease and prevent it.

For some ten years, however, we have attempted without success to develop dental sciences in significant fashion. We estimate that the dental schools of America have a full-time equivalent of approximately 3000 faculty members. Some 800 scientists or their full-time equivalents, including those in dental schools, are applying themselves to dental research. In examining school after school, we could find no "critical mass" of scientists that could sustain work of excellence, and indeed most of the schools had no significant research activity. So we have proposed (and this has been accepted with vigor at six of our stronger universities) the establishment of a full-scale activity in the dental sciences--ranging from morphology and genetics through microbiology, biochemistry and pathology--in an institute framework. This arrangement, which will set out some major goals and apply the talents necessary to achieve them, will provide a setting where older scientists can replenish and expand their skills, where young scientists can be trained, and where big problems can be attacked.

NIH also proposes the establishment of a limited number of institutes of pharmacology and toxicology. When the idea was presented

at a recent meeting of the American Society for Pharmacology and Experimental Therapeutics, opinion was evenly divided. It could be demonstrated, however, that the present departments of pharmacology in large measure have tended to recede from national needs as the medical sciences increased in scope. For example, they were little interested in studying environmental contaminants. Thus it becomes necessary here, as with the dental field, to bring an array of energetic young scientists together--biochemists, organic chemists, mathematicians, biologists, and the like--and to provide a setting where individuals can address themselves to their tasks. As an additional incentive, large amounts of necessary repetitive work would be done on contract rather than wholly within the resources of the medically oriented pharmacologist or toxicologist.

In similar fashion, NIH is developing institutes of developmental sciences, which will engage investigators both biologically and behaviorally oriented. Their work will range from experimental embryology through the morphological sciences. They will study the complicated process of human development, beginning prior to conception and continuing through full development of the child, and in the latter phase will require the clinical skills that are commonly available in departments of obstetrics, gynecology and pediatrics. But the focus will be on development. If left to individual grants within individual

departments, this program would miss the necessary interaction of many skills, the advantages of viewing the same phenomena at different levels of biological organization. The integrated approach is literally impossible within the structure of today's universities and medical schools.

Similarly, we are striving to develop a program to study the aging process, approaching both biological and behavioral aspects in a fashion that will be mutually beneficial.

In the fields of dental science, pharmacology-toxicology, human development, and aging, a systematic effort to develop productive research within the conventional limits of the ordinary departmental structure has met with a notable lack of success. We are therefore developing these new institutional forms in a way that utilizes their potentialities rather than repeating the pattern that has been criticized elsewhere. This approach will involve research on a very broad front. The individual scientist will be able to operate effectively and need not feel submerged by the organization from which his support is derived. The program will provide more extensive opportunities for graduate education than are generally available in our graduate departments today, anticipating the need ten years hence. But what is equally important, this aggregate activity will be serving an identifiable and scientific program with a perceptible social goal. This is the institutional device that we are exploring now in great depth, in the four

areas mentioned above, with a view to determining whether it is possible to satisfy, on the one hand, the driving needs of young scientists and, on the other, a very real and justifiable public pressure. A final objective is to develop this program in a fashion that will strengthen our total scientific establishment.

TAB 63

NATIONAL INSTITUTES OF HEALTH

Background Material for the Secretary of
Health, Education, and Welfare

November 1965

What are the likely areas of future expansion of the National Institutes of Health, particularly in new programs? This is the major question to be considered in the following pages. A brief review of NIH history since World War II will help to clarify the plans and predictions for further development.

In the twenty-year period 1945 to 1965, NIH has undergone a metamorphosis that has transformed its nature and the scope and significance of its activities. In 1945 the tangible attributes of NIH were those of a small in-house Federal laboratory. Its total budget for that year was less than $3.0 million, of which only six percent went to support university scientists. Today, in 1965, NIH is a complex involving nine Institutes, two major program divisions, and an array of supporting activities, with a total annual expenditure of $1 billion for the conduct of research and the support of research, training, and the augmentation of research facilities and resources. As such, NIH administers the world's largest and most advanced set of laboratories and clinics engaged

in medical research, and its funds account for 40 percent of the national expenditures for research in the health sciences and more than one-third of Federal research funds made available to institutions of higher education.

As a consequence of this development, the policies and operations of NIH exert a pervading influence upon the progress of science, the course of academic affairs, and the evolution of public policy in respect to science and health. Thus the twenty-year period may be viewed as the first stage of a development which has brought NIH to a state of maturity, strength, and preparedness for the next major phase of its programs.

The process of past growth may be viewed in four periods:

1945-1950—The initial shape is formed. Significant events that set the stage for the course of subsequent NIH development occurred during the immediate postwar period. In 1944 the Public Health Service Act was enacted, providing basic authority for awarding research grants to non-Federal establishments. The transfer to NIH of residual university contracts from the Office of Scientific Research and Development in 1946 constituted the beginning base of the present-day NIH extramural research support program. By 1950 seven of the nine research institutes which comprise the present-day National Institutes of Health had been authorized and their

programs launched. The total NIH budget had reached $52 million, of which $36 million was being expended in the form of extramural grants and awards for research, training and construction. The national commitment to a scientific attack upon the major diseases had been made.

1951-1955—The framework for action constructed. During this five years the growth in total appropriations was nominal, reaching only about $82 million by fiscal 1955. However, the increase in extramural funds was twice that of intramural. The major effort was to forge the mechanisms, policies, and procedures of extramural support; the processes of review, selection and award of grants; and the relationships with outside advisory groups which still comprise the essential framework for the administration of NIH extramural activities.

The key element in this period of development was the decision, implicit in the study section review and rating process, to concentrate resources upon meritorious research projects in academic institutions. By the end of fiscal 1955, 80 percent of NIH research grant funds were going to colleges and universities. The stage was set for a major expansion.

1956-1960—The years of growth. The guiding concept of this period was that the expansion of medical research in the national interest should not be restricted by lack of funds. This was initiated by Secretary Folsom in fiscal year 1956, ratified by the Bayne-Jones Report in 1958, and acted upon vigorously by the Congress. Between 1955 and 1960, NIH programs expanded over five-fold, reaching a level of $430 million. Investment in the development of resources was substantially enlarged: a matching grant research facility construction program was authorized, and support of training increased by a factor of seven. New fields of scientific endeavor were cultivated. Engagement with science on an international basis became an essential component of NIH programs. By 1960 the period of adolescence in the development of NIH was drawing to a close.

1961-1965—The emerging maturity. In 1961 NIH received appropriations exceeding one-half billions of dollars, and its programs were a significant force in the national scientific scene. Stable support for an institutional base of research and training was enhanced by enactment of general research support authority and initiation of the General Research Support Grant program. The framework for program operation was rounded out by the establishment of the Division of Research Facilities and Resources in 1962 and the National Institutes of General Medical Sciences and of Child Health and Human Development in 1963. The principles, terms, and

conditions governing the extramural program were subjected to reassessment by virtue of congressional inquiry, and a better structured framework for grant administration has emerged.

During this period the pace of appropriation increases was substantially slower. Fiscal 1965 appropriations were only two and one-half times larger than in 1960, but the total amount now exceeds $1 billion. The pace of scientific advance, however, continued to accelerate, and the investment in a broad base of science began to pay off. Now the need to assure effective transfer of capability to the diagnosis, treatment, and prevention of disease and the advancement of health grows urgent. Science stands at the threshold of an "Age of Biology," and medicine is challenged with profound technological and professional changes. This is the setting at the beginning of fiscal 1966 from which NIH must gauge the nature and course of future growth.

The areas of further NIH growth. The mission of the National Institutes of Health, succinctly but broadly stated, is viewed as the advancement of the health and well-being of the American people through scientific effort. The achievement of this mission is sought through pursuit of the following goals:

1. Greater understanding of the biological and behavioral phenomena underlying disease, disability and health through a broad program of investigation of life processes.

2. Advancement of capability for the diagnosis, treatment, and prevention of disease and the maintenance of health through expanded efforts and resources.
3. Acceleration of the effective flow of new knowledge and technological capability from the centers of scientific and academic medicine to the universe of health practice.

Within this framework of purpose and intent the factors that will bear upon the evolvement of NIH and thus the future trend of medical research expenditures can be examined.

Intramural laboratory and clinical research. The further development of NIH is based on the conviction that its direct research activities constitute its essential and vital core. Much of the experience and scientific leadership that NIH has brought to the administration of its national programs has derived from the presence, in the midst of these activities, of a center of scientific excellence and vigor.

So long as the NIH grant programs were largely concerned with strengthening the national research base, the extramural and intramural activities could--and did--remain largely independent. However, due to encouraging scientific progress, more attention can now be given to the deployment of effort for specific program purposes. The time has come when the intramural and extramural programs can function as an interdependent team.

Factors that will influence the scope and magnitude of the NIH intramural effort are the availability of space, the imperative demands of maintaining a position clearly in the vanguard of the advancing biomedical sciences, and the increasing role and significance of intramural capability in the overall direction of Institute programs. Thus planning for the intramural research program will encompass the expansion of activities into the new facilities that will become available. It is estimated that the completion of new research buildings will expand the laboratory area on the main reservation by more than 70 percent in 1967 and 1968. In addition, facilities will be made available at the Animal Center, at Baltimore, and in Puerto Rico. A significant intramural research program is planned for the National Institute of Child Health and Human Development.

The dynamics of academic science. Three-quarters of the expenditures of NIH research grant funds take place in colleges and universities. The support for academic science will continue to be a dominant area of NIH activity, since the advance of basic science remains crucial to successful engagement with the problems of disease and health. The dynamics of growth and change in the academic scene are the consequence of a set of independent forces, such as the rate of population growth expressed in the moving wave of students, the

concommitant expansion of academic and research institutions, the pressing trends in prices and wages, and the effect of advancing sophistication and technology upon the substantive costs of research.

A basic requirement, therefore, in the overall management of NIH programs is the evolution of a stable--but not static--support relationship to this impelling pattern of academic growth and change. The components of this support relationship will encompass:

1. A factor for increase in research project support to meet the needs of new investigators and new ideas.
2. A supplementation factor to correct for the advancing costs of research.
3. Extension of the General Research Support Grant program.
4. Utilization of general research support authority to enlarge the number of centers of excellence in the health sciences.
5. Additional support for training and fellowships to assure at least a constant proportion of manpower flow into the biomedical fields.
6. Securing legislative authorization for a program of career support for research and teaching positions.
7. Provisions for the construction of research facilities and the expansion of research resources.

8. Specific efforts to engender broad institutional planning to anticipate the further expansion of biomedical science, the need to stabilize graduate education in this area, and the enlarging social and service demands impinging upon university medicine.

The emergence of new science. Additional emphasis will be brought to the important NIH role of surveying the developing edge of science. Information will be gained through more concentrated staff efforts, greater use of NIH review panels, the convening of special advisory groups, the operation of information centers in specialized fields, and planned reviews of the state of science in given areas. Through these activities and assessments, areas can be identified where special effort is warranted, and necessary programming efforts can be carried out.

There is great opportunity to exert a major influence upon the rate and direction of scientific development in relation to the objectives of NIH programs. Thus NIH is presently engaged in efforts to stimulate research and training in such problem areas as pharmacology and toxicology, gerontology, and the basic dental sciences, and in such new directions as bioengineering, biomathematics, and the biology of reproduction and development. These special efforts will in turn affect the base of academic science, probably through the development of new institutional forms.

Development and programmatic research. Scientific and technologic advances have generated knowledge, comprehension, and capability applicable to medical problems. The scope of potential contributions to health and medicine from advances in the physical sciences and related engineering and other technology is not fully assessed, but may well be impressive.

The NIH engagement in developmental and programmatic research is already of a distinct and growing dimension in the following program areas:

... Cancer chemotherapy, the oldest and largest developmental activity.

... Special virus-leukemia studies.

... Vaccine development.

... Psychopharmacology.

New and potentially substantial program efforts are in the beginning stages:

... The artificial heart and kidney programs.

... Advanced instrumentation (e.g., ultra-centrifugation) and specialized research environments (e.g., "life islands" and virus-containment facilities).

... Automation of analytical chemistry and other research processes.

... Computer applications to communications, hospital systems, biological simulation, and model construction.

... Telemetry, monitoring systems, and diagnostic aides.

These efforts present a substantial new dimension in NIH programs. They will be reflected in the greater proportion of NIH funds expended for development--applied and programmatic research activities. They will also generate new managerial problems.

For the most part the present framework of NIH for administering research support programs has been developed in the context of the research grant as the principal instrument for support and the community of academic and nonprofit research institutions as the principal resource for scientific effort. In the administration of development programs, the contract will be the principal instrument for support, and the source of scientific and technical capability will be largely private industry. Thus NIH is confronted with the task of bringing into being a framework of operations relevant to the increased contracting for industrial capability. In this area, NIH will expect to draw heavily upon the experience of the Department of Defense and other agencies that have been engaged in large-scale contract programs utilizing industrial capability.

New insights into disease. The characteristics of disease and disability, and of the human mass affected by them, are diverse, complex, and changing. They constitute a vital set of phenomena to be studied for their bearing upon health problems, representing a metamorphosis with profound import for the further course of medical research.

To a very high degree, emphasis and direction of effort in the medical sciences derive from a series of general notions about population characteristics in relation to health and disease. The prospect of vast and far-reaching changes in these basic phenomena emphasizes the need for reconsideration of those notions. Population changes, coupled with increasing technical capability to elicit meaningful information from large masses of data, will give new force to major NIH research programs. New organizational arrangements and more cohesive scientific leadership may be required.

The extension of academic science to the universe of health practice. The extent to which the knowledge, capability, and new technology emerging from research is being brought into effective use in clinical and health services has been a matter of acute concern for some time. Efforts to demonstrate progress under the amorphous label of "communications" have been prominent. Much of this activity has been distracting and has precluded more realistic approaches.

The event that threw new light on the problem of bringing new knowledge and techniques into practice was the release of the report of the President's Commission on Heart Disease, Cancer, and Stroke. The innovative concepts of this report provide for the direct linkage of the centers of scientific and academic medicine with community hospitals and the framework of community medical services, bridging the critical gaps in a most effective and meaningful way.

The legislation that incorporates these recommendations (S. 596 and H.R. 3140), now before the Congress, provides for both planning and operational grants leading to the establishment of medical complexes on a regional basis throughout the country. Each medical complex would encompass a regional medical center having major teaching functions, one or more specialized research centers, and one or more diagnostic and treatment stations. These entities would be linked by exchange of staffs, integrated research and training activities, and programs of continuing education and demonstration. They would reach from the private physician and his patients on the one hand to the advanced research, training, and clinical programs of a university medical center on the other. Knowledge, capability, and technology would flow outward from the centers of academic and scientific medicine, and patients would be speedily referred inward from the community for specialized diagnostic, therapeutic, and research purposes.

These concepts reflect an elegant simplicity and rightness which should exert a pervading influence over the character and quality of medical care available to victims of the three paramount diseases.

The Surgeon General's decision to place the administrative responsibility for this program at the National Institutes of Health will add a major new dimension to the bureau's functions and responsibilities. Additional organizational and operational complexities will be generated. A new operating division and its associated advisory council must be created and staffed; regulations, operating criteria, and procedures must be developed and promulgated; and the coordination of program and operating relationships among various organizational entities must be worked out.

Conclusion

Certainly, the task of adjusting the planning and managerial capabilities of NIH to the above developments will be substantial. A first order of action will be the enlargement and redirection of the program planning functions, both in the Office of the Director and in the several operating programs. A new activity structure for the development and execution of the budget is under study.

The nature of this contemplated program growth will shift the center of gravity of NIH administration from concern with grants management to areas in which Institute and program decisions will be primary. These will involve, for example, the choice of new areas of science for emphasis; the selection of problems for intensive programmatic research efforts; the design of large-scale field studies. Program direction and management of this kind will place a high premium upon scientific and technical judgment, managerial skill, planning and evaluative capabilities. Certain organizational changes may be required.

Extensive and continuing relationships with other Federal agencies are contemplated and will be maintained. Joint planning arrangements among the National Science Foundation, the Office of Education, and the National Institutes of Health have been initiated, and liaison with the Office of Science and Technology is already a well-established practice.

The next five years may well reflect the order of change and increase that occurred in the 1956-1960 period--the youth of NIH. The task will be to ascertain that the strength and promise of that youth are formed into a sound, effective maturity.

TAB 64

Notes for Dr. Shannon's Discussion with
the Corson Committee

I. Background

1. Reference to previous chart presentation and discussion with committee.

2. Emphasize the following

a. Achievement of statutory objective has required assuming responsibility for advancement of the biomedical sciences.

b. This has in turn imposed a concern with the advancement of the relevant professional and graduate education and the institutions and resources therefor.

c. Thus NIH perforce is intimately concerned with the formulation of national policy and programs in science and education.

d. These relationships are complemented by growing applied and developmental activity and the extension of scientific and academic medicine to community practice.

3. Functions, relationships and operating problems of NIH within PHS, DHEW, and the Executive Branch must be viewed in that context.

II. The General Problem of Research and Science in Relation to the Public Health Mission

1. The divergent tendencies--the long term quality of scientific effort versus the urgency of short term health problems.

2. The British arrangement--Medical Research Council (Department of Science and Education) versus the Ministry of Health.

3. The U.S. pattern of mission-oriented agencies in support of the full range of science relevant to their objectives.
4. Thus the position of NIH as a health agency concerned with the use of science in the solution of disease problems and the derived responsibility for advancement of relevant science and graduate education.
5. The consequent importance of close and direct NIH relationships with overall Federal policy and program formulation in science and education.

III. Relationships of NIH and its science role with other parts of the PHS

1. NCHS - Morbidity and Mortality Analysis
2. NLM - Management of information
3. BSS-CH

   Chronic Disease Programs

   Communicable Disease Center

   Grant Referral and Review

   Health Professions Educational Assistance Act

4. BSS-EH

   Relationships in science

5. BMS

   PHS Hospital grants

   Resource for NIH intramural program

   Indian Field Studies

   Quantine - definitions and assessments.

IV. Relationships with HEW

VRA

Childrens Bureau

OE

FDA - Assessment of therapeutic agents

Office of the Secretary

V. Relationships to other Federal Agencies

NSF

AEC

DoD

Agriculture

State

US-Japan Cholera WHO

DoD

Maru

Nutrition

VI. Operating Problems

1. Direct Research

Impediments to excellence--

a. recruitment and retention of personnel

b. View of role and purpose of intramural program

2. Categorical Programs

a. Substitution of political for technical consideration in selecting council members

b. Subordination of program determination to the budget process.

3. Advancement of Science and Education

   a. Distance of NIH formal relationships to the points of overall policy and program determination (OST-BoB-FICE, etc.)

   b. Scope of PHS not commensurate with scope of NIH--PHS excludes much of importance to NIH in science, education, development of institutions, etc.

VI. The Further Growth of NIH

1. The categorical programs.
2. The resource programs.
3. Community relationships
4. Physical sciences, bioengineering and development.
5. Chemical-Biological interaction--assessment of therapeutic agents.
6. Education and science
7. The life sciences
8. International activity

TAB 65

NATIONAL INSTITUTES OF HEALTH

Its Mission, Evolution, Programs and Problems

What are the likely areas of future expansion of the National Institutes of Health, particularly in new programs? This is the major question to be considered in the following pages. A brief review of NIH history since World War II will help to clarify the plans and predictions for further development.

In the twenty-year period 1945 to 1965, NIH has undergone a metamorphosis that has transformed its nature and the scope and significance of its activities. In 1945 the tangible attributes of NIH were those of a small in-house Federal laboratory. Its total budget for that year was less than $3.0 million, of which only six percent went to support university scientists. Today, in 1965, NIH is a complex involving nine Institutes, two major program divisions, and an array of supporting activities, with a total annual expenditure of $1 billion for the conduct of research and the support of research, training, and the augmentation of research facilities and resources. As such, NIH administers the world's largest and most advanced set of laboratories and clinics engaged

in medical research, and its funds account for 40 percent of the national expenditures for research in the health sciences and more than one-third of Federal research funds made available to institutions of higher education.

As a consequence of this development, the policies and operations of NIH exert a pervading influence upon the progress of science, the course of academic affairs, and the evolution of public policy in respect to science and health. Thus the twenty-year period may be viewed as the first stage of a development which has brought NIH to a state of maturity, strength, and preparedness for the next major phase of its programs.

The process of past growth may be viewed in four periods:

1945-1950—The initial shape is formed. Significant events that set the stage for the course of subsequent NIH development occurred during the immediate postwar period. In 1944 the Public Health Service Act was enacted, providing basic authority for awarding research grants to non-Federal establishments. The transfer to NIH of residual university contracts from the Office of Scientific Research and Development in 1946 constituted the beginning base of the present-day NIH extramural research support program. By 1950 seven of the nine research institutes which comprise the present-day National Institutes of Health had been authorized and their

programs launched. The total NIH budget had reached $52 million, of which $36 million was being expended in the form of extramural grants and awards for research, training and construction. The national commitment to a scientific attack upon the major diseases had been made.

1951-1955—The framework for action constructed. During this five years the growth in total appropriations was nominal, reaching only about $82 million by fiscal 1955. However, the increase in extramural funds was twice that of intramural. The major effort was to forge the mechanisms, policies, and procedures of extramural support; the processes of review, selection and award of grants; and the relationships with outside advisory groups which still comprise the essential framework for the administration of NIH extramural activities.

The key element in this period of development was the decision, implicit in the study section review and rating process, to concentrate resources upon meritorious research projects in academic institutions. By the end of fiscal 1955, 80 percent of NIH research grant funds were going to colleges and universities. The stage was set for a major expansion.

1956-1960—The years of growth. The guiding concept of this period was that the expansion of medical research in the national interest should not be restricted by lack of funds. This was initiated by Secretary Folsom in fiscal year 1956, ratified by the Bayne-Jones Report in 1958, and acted upon vigorously by the Congress. Between 1955 and 1960, NIH programs expanded over five-fold, reaching a level of $430 million. Investment in the development of resources was substantially enlarged: a matching grant research facility construction program was authorized, and support of training increased by a factor of seven. New fields of scientific endeavor were cultivated. Engagement with science on an international basis became an essential component of NIH programs. By 1960 the period of adolescence in the development of NIH was drawing to a close.

1961-1965—The emerging maturity. In 1961 NIH received appropriations exceeding one-half billions of dollars, and its programs were a significant force in the national scientific scene. Stable support for an institutional base of research and training was enhanced by enactment of general research support authority and initiation of the General Research Support Grant program. The framework for program operation was rounded out by the establishment of the Division of Research Facilities and Resources in 1962 and the National Institutes of General Medical Sciences and of Child Health and Human Development in 1963. The principles, terms, and

conditions governing the extramural program were subjected to reassessment by virtue of congressional inquiry, and a better structured framework for grant administration has emerged.

During this period the pace of appropriation increases was substantially slower. Fiscal 1965 appropriations were only two and one-half times larger than in 1960, but the total amount now exceeds $1 billion. The pace of scientific advance, however, continued to accelerate, and the investment in a broad base of science began to pay off. Now the need to assure effective transfer of capability to the diagnosis, treatment, and prevention of disease and the advancement of health grows urgent. Science stands at the threshold of an "Age of Biology," and medicine is challenged with profound technological and professional changes. This is the setting at the beginning of fiscal 1966 from which NIH must gauge the nature and course of future growth.

The areas of further NIH growth. The mission of the National Institutes of Health, succinctly but broadly stated, is viewed as the advancement of the health and well-being of the American people through scientific effort. The achievement of this mission is sought through pursuit of the following goals:

1. Greater understanding of the biological and behavioral phenomena underlying disease, disability and health through a broad program of investigation of life processes.

2. Advancement of capability for the diagnosis, treatment, and prevention of disease and the maintenance of health through expanded efforts and resources.
3. Acceleration of the effective flow of new knowledge and technological capability from the centers of scientific and academic medicine to the universe of health practice.

Within this framework of purpose and intent the factors that will bear upon the evolvement of NIH and thus the future trend of medical research expenditures can be examined.

Intramural laboratory and clinical research. The further development of NIH is based on the conviction that its direct research activities constitute its essential and vital core. Much of the experience and scientific leadership that NIH has brought to the administration of its national programs has derived from the presence, in the midst of these activities, of a center of scientific excellence and vigor.

So long as the NIH grant programs were largely concerned with strengthening the national research base, the extramural and intramural activities could--and did--remain largely independent. However, due to encouraging scientific progress, more attention can now be given to the deployment of effort for specific program purposes. The time has come when the intramural and extramural programs can function as an interdependent team.

Factors that will influence the scope and magnitude of the NIH intramural effort are the availability of space, the imperative demands of maintaining a position clearly in the vanguard of the advancing biomedical sciences, and the increasing role and significance of intramural capability in the overall direction of Institute programs. Thus planning for the intramural research program will encompass the expansion of activities into the new facilities that will become available. It is estimated that the completion of new research buildings will expand the laboratory area on the main reservation by more than 70 percent in 1967 and 1968. In addition, facilities will be made available at the Animal Center, at Baltimore, and in Puerto Rico. A significant intramural research program is planned for the National Institute of Child Health and Human Development.

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THE MISSION OF NIH

ADVANCEMENT OF HEALTH AND WELL-BEING OF THE AMERICAN PEOPLE THROUGH SCIENTIFIC EFFORT. THE GOALS SOUGHT:

- GREATER UNDERSTANDING OF THE BIOLOGICAL AND BEHAVIORAL PHENOMENA UNDERLYING HEALTH AND DISEASE
- ADVANCEMENT OF CAPABILITY FOR THE DIAGNOSIS, TREATMENT AND PREVENTION OF DISEASE AND THE MAINTENANCE OF HEALTH
- ACCELERATION OF THE FLOW OF NEW KNOWLEDGE AND TECHNOLOGY FROM MEDICAL CENTERS TO THE UNIVERSE OF PRACTICE

FUTURE NIH EFFORTS WILL BE CONDITIONED BY—

- ADVANCING THE EXCELLENCE OF THE INTRAMURAL RESEARCH PROGRAM
- THE DYNAMICS OF GRADUATE EDUCATION AND ACADEMIC SCIENCE
- EMERGENCE OF NEW SCIENCE
- NEW INSIGHTS INTO DISEASE PHENOMENA
- OPPORTUNITIES FOR APPLIED RESEARCH AND DEVELOPMENT
- MOVEMENT OF KNOWLEDGE AND TECHNOLOGY TO THE COMMUNITY SETTING

ADVANCING THE EXCELLENCE OF THE INTRAMURAL RESEARCH PROGRAM

- NEW FACILITIES FOR—

  national institute of mental health

  national institute of neurological diseases and blindness

  national cancer institute

  division of biologics standards

  division of computer research and technology

  NIH library, freeing space in clinical center

- ADDITIONAL SPACE AT—

  animal center

  gerontology buildings at Baltimore

  perinatal research laboratory at Puerto Rico

- INTRAMURAL RESEARCH PROGRAM FOR—

  national institute of child health and human development

- CAPABILITY TO INTEREST AND RETAIN MEN OF EXCELLENCE

THE DYNAMICS OF ACADEMIC SCIENCE, GRADUATE EDUCATION AND THE INSTITUTIONAL BASE

- CONDITIONED BY THE PROCESSES OF GROWTH AND CHANGE

  population growth expressed in moving wave of students

  expansion of academic and research institutions

  increasing social role of academic institutions

  trends in research costs:

    price-wage change

    increasing complexity and technology of science

- CALL FOR STABLE SUPPORT THRU—

  factor to accommodate new scientists and ideas

  factor to meet advancing costs of research in the committed base

  extension of general research support grant program

  provision for research and teaching careers

- CALL FOR EXPANSION OF SUPPORT FOR—

  expanding institutional capability in the health sciences

  training, facilities and other resources

  broad institutional planning

EMERGENCE OF NEW SCIENCE

- EMPHASIS ON SURVEYING THE SCIENTIFIC FRONTIER

  to identify where to put special effort

  to guide in developing programs

- OPPORTUNITY TO POINT ACADEMIC EFFORT TOWARD NIH GOALS IN—

  pharmacology and toxicology

  gerontology

  basic dental sciences

  biology of reproduction and development

  extending physics, mathematics and engineering to biology and medicine

- THESE SPECIAL EFFORTS WILL AFFECT BASE OF ACADEMIC SCIENCE THRU—

  expansion of research and training support

  emergence of new departments

  development of new institutional forms

OPPORTUNITIES FOR APPLIED RESEARCH AND DEVELOPMENT

- NIH INCREASINGLY SUPPORTS APPLIED AND DEVELOPMENTAL EFFORTS IN—

  cancer chemotherapy

  special virus-leukemia studies

  vaccine development

  pharmacology

- NEW EFFORTS ARE BEGINNING IN—

  artificial organ programs

  advanced instrumentation

  automation of analytical chemistry and other processes

  computer applications

  telemetry, monitoring systems, diagnostic aids

- WILL REQUIRE NEW ADMINISTRATIVE MECHANISMS

  greater use of research contracts

  new provisions for qualitative review

NEW INSIGHTS INTO DISEASE PHENOMENA

- CHARACTERISTICS OF DISEASE ARE COMPLEX AND CHANGING

  patterns of birth and death rates, acceleration of population growth, changing age composition

  genetic patterns and composition of population

  mobility and distribution of populations

- SOCIAL AND ECONOMIC VS. THE BIOLOGICAL DETERMINANTS OF ILL HEALTH

- NEW STATISTICAL THEORY AND MASS DATA-PROCESSING CAPABILITY

  increase ability to search for information in large masses of data

  open new prospects for research programs

  may call for new organizational arrangements and more cohesive leadership

MOVEMENT OF KNOWLEDGE AND TECHNOLOGY TO THE COMMUNITY SETTING

- REGIONAL MEDICAL PROGRAM

  an answer to problem of communications in health and health science fields

  would directly link medical and research centers with community services

  based on locally devised cooperative arrangements

- NEW DIVISION PROJECTED

  national advisory council

  regulations, operating criteria, procedures

  coordination of program and operating relationships to be worked out

THE PRESSING ADMINISTRATIVE PROBLEMS

- SELECTION AND USE OF ADVISORY COUNCILS AND CONSULTANTS
- THE PROCESS OF APPOINTMENT OF KEY STAFF
- SALARY LIMITATIONS
- ACCESS TO BUDGET DECISION-MAKING AFFECTING PROGRAM CONTENT

TAB 66

Speech file

#390

JAShannon
November 30, 1965

A FRAMEWORK FOR THE ASSESSMENT OF THERAPEUTIC AGENTS
A Proposal for Discussion with the Surgeon General

The Problem

The Kefauver-Harris Drug Amendments of 1962 imposed broad responsibility on the Secretary of Health, Education, and Welfare in respect to the evaluation and control of drugs, both new and in current use. The amendments strengthened substantially the authority and responsibility of the Secretary of HEW by requiring that both efficacy and safety be established as the basis for licensure of a new drug.

The laboratory and clinical information available at the time of granting a new drug application is necessarily limited. Therapeutic trials may include a few hundred to several thousand cases. As the drug gains the acceptance of the medical profession, the number of patients receiving the drug may increase by one or two orders of magnitude in a comparatively short period. Untoward reactions appear which could not have been predicted on the basis of the limited experience obtained during the developmental phase. This would seem to be an inevitable consequence of the introduction of a new therapeutic ~~modality~~ agent into widespread use. This type of experience generates conflicting opinions, of a serious nature and an array of complicated problems emerge which require a new and different ~~modality~~ approach for their solution than currently exists. A framework for examining the pharmacological and toxicological attributes of drugs, including the conduct of highly specific clinical trials, necessitates a setting wholly apart from the licensing and regulating process which produce an adversary relationship between FDA and the industrial group.

The scientific diversity of current problems at issue, as well as those that may be anticipated as the result of a well equipped and scientifically diverse industry, makes it unlikely that the public interest will be adequately served by mechanisms otherwise well suited to the operation of a regulatory agency. A way must be found for extensive involvement of important elements of the academic world without at the same time projecting the university scientist into the pressing problems of the regulatory process itself. If a suitable mechanism can be developed it should then be possible to acquire objective evidence of the net value of a candidate therapeutic agent during the preliminary extension of the drug to substantial population groups. It should also be possible, in the long term, to develop, by direct approach, a systemization of chemical-biological interactions, which will permit, at the very least, some limited generalizations which serve as a more rational base for the examination of both therapeutic activity and toxicity of medicinals (See attachment I).

The Elements of a Solution

The National Institutes of Health is extensively involved both in its direct research activities and through its grant and contract programs in many if not most aspects of drug, clinical testing and evaluation.

The direct operation at Bethesda contains the highest concentration of truly superior scientists in these areas in the Nation; these are

particularly concentrated in the Heart Institute, the Cancer Institute and the Institute of Mental Health. Other Institutes contain excellence in these fields but to a lesser extent. [Extensive experience and a substantial capability exists in this complex area.]

The NIH grant programs have supported and are further increasing academic capability in these fields in two ways. Through NIH programs directed towards the expansion of clinical research facilities throughout the Nation, resources for clinical investigation have been substantially enhanced and enlarged. The new program to strengthen the fields of pharmacology and toxicology is now bringing into being major centers for research in the area of chemical-biological interaction. [Comment]

These activities provide an extraordinary background for the development of a new framework to undertake broad tasks in the scientific assessment of therapeutic agents. This framework can be made to serve the critical needs of the Secretary of HEW in respect to problems of new drugs in those extraordinary circumstances where the existing arrangements within the Food and Drug Administration are not sufficient to resolve the matters at issue.

Such a framework would involve the following elements:

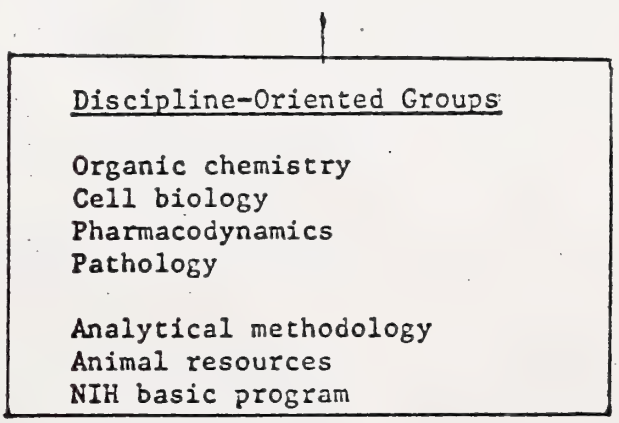
1. Basic Science Components. The scientific setting for the assessment of therapeutic agents requires as a basic component a series of discipline-oriented groups. Essential among these are the following:

Organic chemistry
Cell biology
Pharmacodynamics
Pathology (including microstructure)

Beyond these basic disciplines which constitute the core of the laboratory inquiry into the phenomena of chemical-biological interaction, certain resources are needed.

There must be intimate access to a broad analytical capability and methodology for the precise ~~qualitative~~ quantitative determinations of the nature, distribution and metabolic transformation of exogenous substances introduced into biological systems. There must also be a capability for examining the qualitative and quantitative modification of the biological components of the system affected. Specialized animal resources must also be available to provide highly stable genetically standardized experimental animals for study purposes. Physical resources must permit both short term and very long term observations particularly designed to exclude intrusion of extraneous factors such as viruses and unintentionally introduced chemical and physical agents. These are particularly pertinent to the increasingly current problems of long term exposure to low levels of prospective biologically active agents. The basic program of the NIH at Bethesda is well suited to assist such a development.

The basic disciplinary groups and their supporting resources are the essential beginning of a framework for the assessment of therapeutic agents as follows:



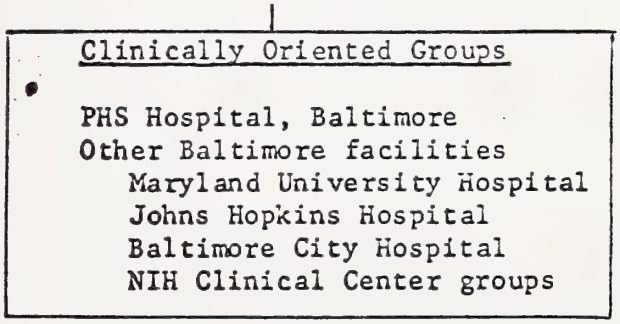
Building upon the present diverse engagement in these areas, a purposely directed component could be created for the precise purpose of developing the NIH capability to administer a broad therapeutic trials program.

2. Clinically oriented groups. The essential complement to the basic discipline oriented groups in such a framework is the availability of clinical research facilities sufficient to provide access to the substantial numbers and wide diversity of clinical material required for the critical observation and assessment of a variety of drug actions in the human being. The National Institutes of Health is currently involved in a modest expansion of clinical investigation facilities at the PHS Hospital in Baltimore in connection with the solid tumor programs of the National Cancer Institute. This hospital, its present physical facilities and the availability of additional space for essential construction can soon provide a physical setting for the combined resources of both discipline-oriented groups and purposely developed clinical groups for an effective program.

It can be stated with some assurance that such a resource at the Baltimore PHS Hospital could be supplemented by other clinical research facilities in the Baltimore area. Negotiation would be required with the University of Maryland Hospital, The Johns Hopkins Hospital, and The Baltimore City Hospital. In each of these institutions NIH is currently supporting extensive clinical research activity. This research activity already involves clinical research units which can be expanded and a

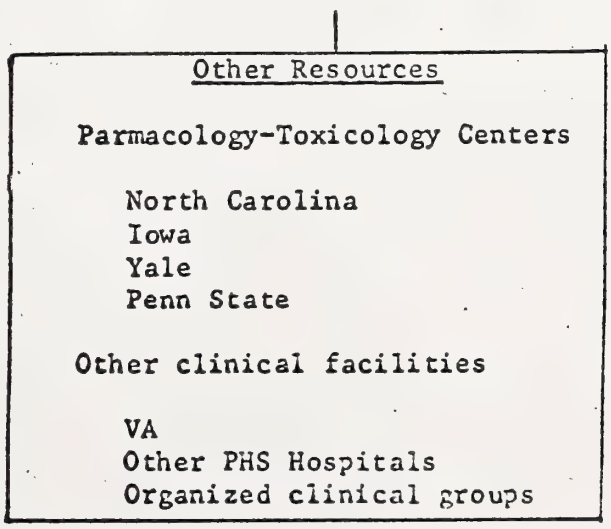
number of specialty clinical groups that could be brought into the program. Thus it would be possible to develop in Baltimore, utilizing the PHS Hospital as a base, a correlated group of clinical resources which would provide for the scale and diversity of clinical and laboratory needs necessary for the conduct of a therapeutic trials program.

The plan would be to support, at least in part, the maintenance of a number of specialty groups composed of both in and out patients. Although, undoubtedly, such groups would be utilized for research purposes of primary interest to the institution concerned, the support mechanism utilized would be negotiated in a manner which would permit ready access to the groups for specific therapeutic trial purposes. Comparable groups of patients would also be available, but in lesser numbers, in our own clinical setting in Bethesda. Organizationally such a general activity would appear as follows:

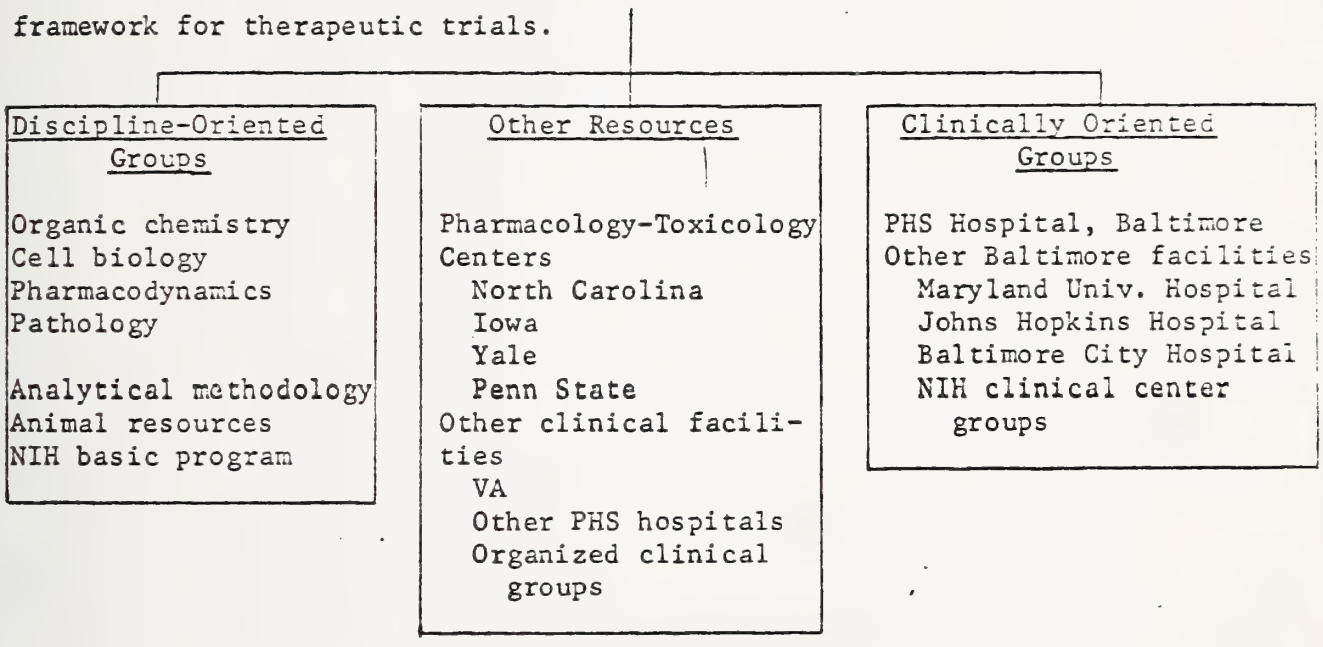


3. Other resources. Other scientific resources which can be drawn upon to supplement substantially the proposed programmatic development at Baltimore. Important among these other resources are the pharmacology and toxicology centers resulting from the awards made or proposed under the NIH program in this area. Particularly suited environments for such

collaboration must have as an essential component a broad base of related laboratory work, access to and potentially close association with diverse clinical groups of patients with a variety of disease entities. Potential participants in such an association include the following institutions: North Carolina, Iowa, Penn State and Yale. An effort has been made to assure access to adequate clinical research facilities to complement the basic science work and also to emphasize the national role that the centers are expected to serve in the conduct of their programs. In addition to such center facilities and depending upon the nature of needs and requirements that might emerge in the conduct of a broad therapeutic trials program, it seems clear that use could be made of the facilities of other PHS Hospitals and without doubt successful negotiations for inclusion would be possible in the cases of the Veterans Administration Clinical Organization, the Permanente Foundation on the West Coast, the ILGWU Program in New York City, etc. Organizationally such groups could be grouped as follows:



The array of discipline-oriented groups complemented by clinical research capabilities available in the Baltimore area and supplemented by broad laboratory and clinical resources now being developed under the pharmacology-toxicology program could, with suitable negotiations, constitute the substantive scientific level of activities in an overall framework for therapeutic trials.



The effective utilization of capability at the scientific level for the solution of very practical and pressing problems with high technical content would require certain essential staff and managerial functions. Such services might be grouped as follows:

1. Biometrics. The conduct of studies, both at the basic science level and in the clinical setting, aimed at discerning differential qualities, both therapeutic and toxicologic, of drugs and other therapeutic agents requires high capability in the field of biometrics, experimental design and new mathematical and statistical concepts such as information theory and the Bayesian approach to the resolution of uncertainty.

Emphasis upon long term studies involving animals and human cohorts for the observation of longitudinal change under varying levels of exposure to drugs similarly demand rigorous biometric design, precise data collection and complex analysis of multiple variables. Therefore, an essential staff component of this framework would be a sophisticated biometrics group.

2. Information center. Means for collection, storage, and retrieval of information relating to the biological activity of chemical substances is another essential staff function in the conduct of a therapeutic trial program. At the present moment the National Institutes of Health is supporting, in conjunction with several other Federal agencies, a major project centered upon the codification of chemicals in relationship to biological activity being conducted by the American Chemical Society. Systematic recording and analysis of the interrelationships between chemical structure and biological activity may eventually lead to a higher degree to rationality and predictability in the development of new therapeutic agents. Through the study of such relationships it is hoped that a broader knowledge of the nature of chemical-biological interaction can be evolved.

Of equal importance is the need to provide through the "secondary literature" a more adequate portrayal of the therapeutic opportunities and hazards of chemical agents as these properties are assessed. It is necessary to support more broadly such activities as the current "news letters" and categorical issuances of the Institutes and others

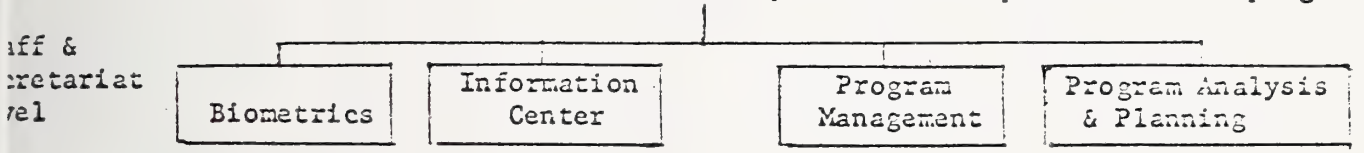
on therapeutic agents. The resources of the National Library of Medicine must be purposely addressed to the problem of regrouping the abstract literature on the dual grids of the characteristics of individual and groups of therapeutic agents and disease problems modifiable through the use of diverse therapeutic agents. Finally, such information must be made more readily available to the student, the practitioner and the scientist alike through the development of a series of authoritative monographs.

3. Program management. The conduct of a complex program in therapeutic trials will involve the logistical support of discipline-oriented laboratories, clinical research facilities and extensive contractual relationships with other research facilities and resources. The conduct of this program will therefore require able managerial skills and resources. A program management staff thus becomes another important component at the staff and secretariat level of this program.

4. Planning and program analysis. The framework for assessment of therapeutic agents is in essence designed as a problem-solving organization. However, its functions must necessarily involve both specific tasks of assessment and, most importantly, a broad base of continuing scientific activity directed toward the evolution of new concepts of drug therapy, the theory of drug action, and more effective protocols and arrangements for the assessment of therapeutic agents. The continued improvement of this program, the further development of the design concepts, and the careful assessment of the results that have been achieved in past efforts is a continuing important function

to be purposely carried out by a separate program planning and analysis group.

The above four components would constitute the staff and secretariat level in support of the conduct of the substantive scientific activities of the basic disciplinary and clinically oriented components of the program.



The overall direction of this program would be through a director, a senior scientist with a broad background in pharmacology, the development of therapeutic agents, and the design and direction of assessment programs. The functions of the Director of this therapeutic trial program would be supported by arrangements to draw upon nonfederal scientific and technical judgment and capability. Two groups would be established for this purpose:

1. The Therapeutic Trials Board. This Board, comprised of the best available scientists, knowledgeable in the broad fields of pharmacology, toxicology, and the development and assessment of therapeutic agents, would serve theprincipal function of determining the need, advisability, and feasibility of submitting a particular therapeutic agent to broad assessment through the scientific activities of the trials program. This group, after review of the materials relating to the experimental development and use of a therapeutic agent in question would reach the judgment whether further laboratory or clinical assessment was necessary to establish disputed facts in respect to the efficacy, safety, and therapeutic

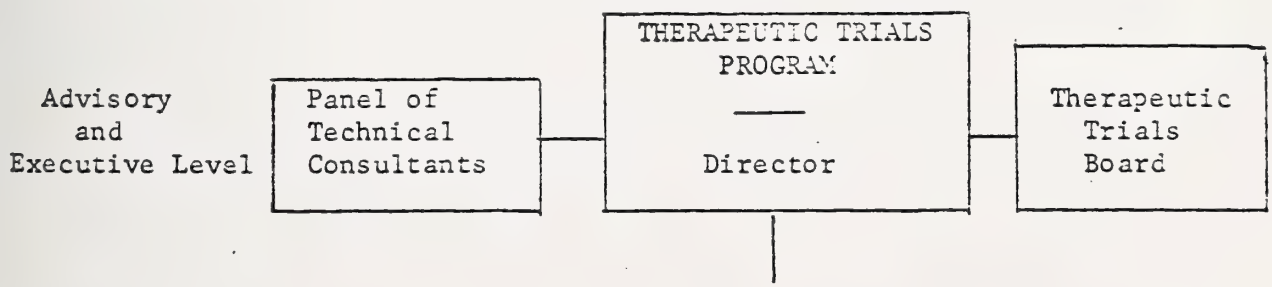
capability of the drug. The advice of this group would be made available to the director for his executive determination of the action to be taken in respect to the agent in question.

The nature of the actions of the Board, together with the environment of controversy within which it would generally operate, requires that it have clear visibility and the results of its deliberations not be restricted to internal use.

2. Panel of Technical consultants. The work of the Therapeutic Trial Board would be supplemented by a panel of technical consultants covering the full range of scientific and technical ability relative to the assessment of therapeutic agents whose services could be called upon either by the director or by the Therapeutic Trial Board to provide scientific and technical consultation in the reaching of judgments.

The professional units involved in the general collaborative program would be particularly suitable for providing one source of technical and professional consultation. Services from the staff and secretariat level should be made freely available to the Board by the Director who should be responsive to the needs for staff studies on particular subjects.

Organizationally the Board and panels of technical consultants would function as advisors to the director as follows:

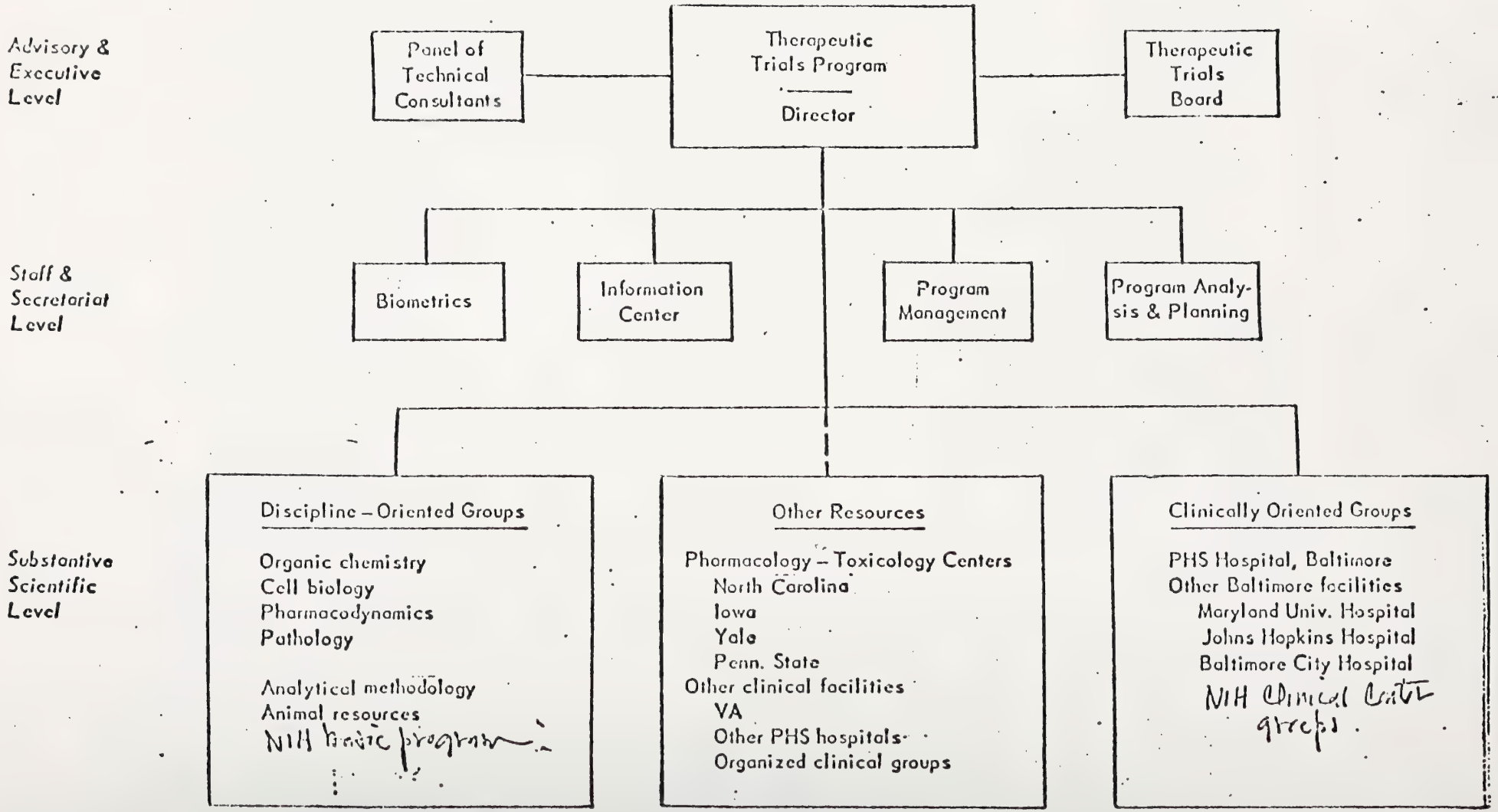


An important feature of the employment of nonfederal scientists on both the Therapeutics Trial Board, and the panel of consultants would be an arrangement by means of which the individuals so utilized could be paid a retainer no less than $5,000 a year to make it possible for such individuals to divest themselves of all consultancy arrangements with industrial organizations whose products or activities might be subject to examination within this framework. Such a retainer relationship would make it possible to bring to the conduct of this therapeutic trials program the senior judgment of the scientific community which, at the present time, is now heavily involved in industrial activity. Similarly, grants and contracts to collaborating groups could provide funds in support of individual scientists on a total income basis and so achieve freedom of conflict of interest on the part of all collaborating scientists.

This advisory and executive level would complete the total framework of the therapeutics trails program. It would function as a component of the National Institutes of Health, headquartered in new facilities to be developed on the grounds of the Public Health Service Hospital in Baltimore, and would serve as the national mechanism for the resolution of critical problems surrounding the introduction and use of new therapeutic agents.

The structural relations among the various elements of the program would be as follows:

FRAMEWORK FOR ASSESSMENT OF THERAPEUTIC AGENTS



The Circumstances of Use

The manner in and the circumstances under which this therapeutic trial program would be brought into play are an important consideration. First, it is important to emphasize that this program would have a set of scientific objectives in its own right. These objectives although not of first priority would be centered around the purposeful exploration of the phenomena of therapeutic action aimed at contributing to the development of more rational concepts of drug action and the eventual formulation of new theory relating to chemical and biological activity. Resources should be adequate so that such a program would have adequate scope and opportunity. The utilization of this framework for specific therapeutic trials would result from a specific direction from the Secretary of Health, Education, and Welfare who would seek the assistance of the therapeutic trial board in the resolution of problems of the following nature:

1. The assessment of the characteristics of a drug for which a drug application has been made and for which a major difference in judgment between the Food and Drug Administration and the sponsor of the drug has developed in the normal process of review and licensure. In these circumstances the Therapeutic Trial Board would be asked to determine whether the evidence available would require further scientific assessment of the drug or whether, indeed, the evidence would substantiate a negative action in respect to a particular new drug application.

2. The emergence of critical problems relating to adverse side effects of therapeutic agents now in use which are of such nature that the Secretary of Health, Education and Welfare may require an independent assessment of the hazard or other toxicological characteristics of a drug as a basis of determining the nature of control action in respect to the further use or commercial distribution of the agent. In these circumstances again the Therapeutic Trial Board would make the initial judgment as to appropriate action needed utilizing the framework of the therapeutic trial program.

3. The periodic review of classes or groups of drugs to assess their identity and strength, quality and purity characteristics, and the efficacy of such drugs for their purported use as a part of a major reassessment of the therapeutic armamentarium of present day medicine. The precise nature of the full functions of this organization beyond its basic scientific program would obviously be subject to further modification and evolution as the role of this framework was evaluated in the context of national needs.

The policy, legislative, and appropriation implications

The development and conduct of this framework for assessment of therapeutic agents obviously presents major policy problems, the most critical of which are the precise circumstances of its use. It is not

intended that this program would be used for the development of new drugs nor would it be generally used for the testing of all new drugs proposed for licensure. To the maximum extent possible the use of this framework would be invoked only by the Secretary of HEW for the resolution of critical questions which, as a result of continued efforts in the normal framework of the Food and Drug Administration, have not been resolved. It would provide the scientific capability for scientific assessment essential to the final resolution of drug problems in a setting separate from the adversaries context of the Food and Drug Administration relationships with the pharmaceutical industry. Thus its role would have to have broad acceptance both by the Federal agencies involved and the industry whose products would be submitted to its judgment. The conduct of this program in terms of the activities to be carried out does not at this stage, present any legislative or statutory problems. All of the specific functions proposed seem to be within the legislative authorities of the Public Health Service and the Secretary of HEW. The role of such a framework, of course, in the process of drug and control may or may not require legislative concurrence.

This framework obviously would require a major expansion of staff of the NIH, the development of specialized facilities at the Baltimore PHS hospital and broad contractual and consultancy relationships. These, indeed, would generate new appropriation requirements, the dimensions of which have not yet been measured.

Finally serious consideration has been given to the possibility of utilizing the NIH as presently constituted for the purposes defined in this document. A judgment has been made that the framework proposed could not operate except as an extension of the currently broad commitment of the staff of NIH to pharmacology, toxicology, and the development and assessment of therapeutic agents.

~~Summary~~ reasons for the inability of the NIH in this respect could be developed at length but are amenable to summary statement as follows:

1. The programs of the NIH are categorically oriented and the groups most suited for inclusion in the activity under consideration are already discharging a function in the absence of which the proposed program could not be mounted.

2. The bed capacity of the clinical center is inadequate to subserve the important categorical objectives of the Institute and at the same time serve as the clinical base for a broad national program of suitable diversity as proposed.

3. NIH does not have available either diverse or substantial clinical groups of out patients, such as are characteristic of the usual University Hospital setting. Some of these could be set up in Baltimore (PHS Hospital) but still prime dependence would be on University or City clinic groups.

4. There is need of broad academic involvement relating, within a given geographical area, fundamental scientific disciplines and several associated hospital settings such as proposed for Baltimore. (This type of association does not preclude the development of local competence in

a number of scientific disciplines within the hospital setting or indeed such a development in the long run would be essential.)

5. An essential for success of the endeavor is that an organization ideally suited to the problems which will be posed must be designed and developed without compromise. Another course is deemed certain of failure. In the case of NIH, to accept such a responsibility within the existing NIH structure would result in serious disruption of a highly effective program now in being with no assurance of developing the proposed effective problem solving mechanism.

TAB 67

Dr. S. John Reisman
Executive Secretary
National Advisory Health Council
Director
National Institutes of Health

February 10, 1966

Transcript of Proceedings of December Meeting of the Health Council

I believe that the transcript would be more clear and could serve a better purpose were my remarks recorded as edited. A clear copy is provided for this purpose.

(Sgd) James A. Shannon

James A. Shannon, M.D.

Attachment

cc: Mrs. Scott
Mr. Carrigan
Mr. Murtaugh

VERexroth:sds

Mr. Carrigan

Before we go on to Jim Shannon, I might read you two paragraphs of the letter which I sent to Senator Javits.

"In addition to discussing these steps--and these were the steps that Jim told you about last time--a notice with the award, and I have forgotten what the other step was--study sections being directed to look into this, Dr. Shannon also proposed for consideration by the National Advisory Council a draft resolution concerning the exercise of ethical and moral judgment in the conduct of clinical investigation to provide for the promulgation of certain principles which should apply in all circumstances involving observation or investigation utilizing human beings regardless of the sources of support or other circumstances attendant upon the conduct of research activity. A draft copy of this proposed resolution is attached for your information.

"The National Advisory Health Council expressed its serious concern with these matters, stated its approval of the steps thus far taken by NIH in the conduct of its programs and expressed the desire to study carefully the proposed resolution, to discuss it within their own institutional environment, and to conduct the examination of this matter with the clear intent of reaching a conclusive standpoint in the next series of meetings of the Council scheduled for December 1965."

DR. SHANNON: I thought, Bill, that it would be clarified, and didn't worry about the resolution; however, I recommend that you read it. You

will note that this resolution is very limited, simply stating, "Clinical investigation involving hazard should be undertaken only with concurrence of judgment by a group of peers within the institution." You have it before you. It is on page 2, beginning at the bottom of the page. I don't think this resolution would be embarrassing, as it is quite limited in scope.

DR. BRANSCOMB: Dr. Shannon, why is the reference to informed consent not touched upon in the resolution?

DR. SHANNON: I think it should be.

MR. MURTAUGH: Jim, may I?

This was aimed at establishing the responsibility of the granting agency in this respect.

DR. BRANSCOMB: I know, but in reading it, I was struck by the fact that this resolution does conform to exactly what Mr. Odegaard was saying. It does not say anything about this is a resolution for granting agencies only. It is very general and sweeping. And, therefore, it is applicable to the whole ethical standard to be employed, not merely to the protection of the granting agency the way it is worded here.

DR. SHANNON: This is for your consideration, sir. And it is precisely what we want.

DR. STEWART: Dr. Odegaard.

DR. ODEGAARD: Since I was making the remarks before our meeting began to which Dr. Branscomb has alluded, I would like to repeat, if I may, the point of my question.

I feel that so far as the Council is concerned, it can only commend the officers of the Public Health Service and the NIH for their concern in this matter. It seems to me that the Council should make a recommendation in this area.

However, I have a question as to the ultimate handling of this problem which I would like to place on the table now. It would seem to me there should be a protocol--is that the correct phraseology--with reference to clinical investigation which would be established, hopefully, with the collaboration of all those concerned with medical investigation. And certainly, as a minimum, there should be such a protocol with reference to federally supported activities. But it would be desirable if that protocol could ultimately be achieved in collaboration with, you might say, all the various interested agencies, parties, institutions, engaged in medical clinical investigation.

Therefore, I wonder if there is a kind of first step looking toward a second step which could be taken. The first step might be an agreement tentatively, so to speak, on a protocol in which I would think the point which has been made by Dr. Branscomb with regard to informed consent might be added to the text of the draft resolution which is under discussion and that, then, NIH officers might endeavor in consultation with appropriate representatives of other agencies concerned with clinical investigation to arrive at consent on such a text.

What I have in mind is ultimately the desirability of a standard regulation here which would be applied, not only by the Federal agencies responsible, but by all parties responsible for clinical investigation. That would mean, then, that the text itself might be adopted, for example, in a tentative form first, subject to further consultation and then review or perhaps final adoption by the National Advisory Health Council as a recommendation to the NIH for the conduct of its grant activities.

DR. STEWART: Dr. Odegaard, may I ask you a question on the development of such a protocol?

Do you think that in developing this protocol, we should have what you might call inputs into the development of it from the fields of law and from religion and from informed laymen as well as the scientists and physicians and others who are involved in clinical investigation?

DR. ODEGAARD: In terms of the ultimate validity of this as a guide for conduct of affairs in this area, I would think it would be desirable if possible to seek such participation because, in the last analysis, we are dealing here with the matter of the public conscience and persons other than clinical investigators are involved in that process, I take it.

On the other hand, there is a sense of responsibility abundantly manifest in the way in which the Service has presented this problem to the Council. And whether ultimately the participation of all these parties can be achieved effectively or not, I think we have already heard enough

to feel there is a responsibility here to act in any case, but that's why I am suggesting that there be a kind of tentative aspect to the statement as first adopted here in the hope that a wide consent to a text perhaps somewhat modified and in turn found acceptable by the NIH and the Council and the Federal government.

DR. WOLFLE: I would like to raise a caution about the possibility of putting in any wording here concerning consent. There is a problem of establishing a proper standard involving consent and other ethical issues. There is also a problem of procedure for making certain that good conduct is exhibited by investigators.

And this resolution addresses itself to the latter problem. It does not address itself to the former except in quite general terms that the risk benefit of the scientific work involved and the maximum protection of the rights and welfare of the individual or individuals.

And it seems to me this is as far as we should go here. If we try to write out the rules in here, we are adding another document. And I don't think we want to do it just in terms of consent. This resolution as it stands, in essence, says that the responsibility of judgment should not be borne individually; that the institution is responsible for establishing procedures so there will be good informed peer judgment. And this is a procedural matter, and I think a good one. It leaves aside some of these other questions to be taken in another paragraph.

DR. STEWART: It might be that it fits into what Dr. Odegaard was saying. While we need to develop the protocol we do have a responsibility to do what we can now. And this is a procedural suggestion that is being made here on what can be done now.

As far as the protocol goes, Dr. Odegaard, we have in mind taking a couple of steps.

One, Dr. Shannon is going to call together a group who represents those areas that I mentioned plus others, not for the process of developing the protocol, but really to get their advice on how you go about getting such a protocol developed with the varied interests and--well, this public conscience represented in the development of protocol--where it should be done by whom. And I don't know whether this meeting is scheduled or--

DR. SHANNON: No. I wanted to talk to you about it. However, there is no reason not to make the proposal at this time.

Bill said to go ahead about a week or ten days ago with the development of this group--with the general discussion. We propose to select an appropriate non-Federal social agency to serve as the focal point for these discussions. The most suitable, it seems to me, would be an organization such as the National Academy of Arts and Sciences, one of our most distinguished professional organizations--one that encompasses a broad array of professions drawn from religious, legal, scientific, and cultural spheres of activity.

The thought occurred to me later--and I commend it to the Council's consideration--that the Academy issues a quarterly periodical called Daedelus, D-a-e-d-e-l-u-s, devoted to present-day social problems. The most recent issue addressed itself, in a series of very thoughtful articles, to the problems of the American Negro. This was the first series of scientifically valid, socially sound comments on the subject that I have read which really tried to explore the facts, the circumstances, and potential solutions. The next issue of Daedelus will be devoted to discussions that have been stimulated as a result of the previous publication.

The organization, its journal, and the professionals who cooperate in its development have a profound effect on social thinking. It should be pointed out that the National Academy of Arts and Sciences sponsored the group that laid the groundwork for our present efforts in disarmament and for the nuclear test ban.

As I say, this organization is ideally suited to an examination of a broad spectrum of attitudes. At the present time, they are developing a volume that will attempt to outline the social choices available during the 1960's which will influence our social structure during the next decade. They are made up of sociologists, economists, scientists, technologists, engineers, and the like.

It occurs to me that we could go to the Academy in the present instance. One circumstance that might be very much to our advantage is that the president of the National Academy is probably one of the most thoughtful jurists presently addressing himself to broad social problems.

DR. KENNEDY: Paul Freund.

DR. SHANNON: Yes, I think Dr. Freund would be delighted to use this apparatus--first to undertake general discussions, and then to decide the best matrix within which these thoughts might be expressed.

As I have pointed out, there is the distinction of the organization, as well as its broad accomplishments in the past in dealing with a variety of religious, social, and scientific attitudes. It might be that a volume addressed to the matter at hand would have a profound effect on the social conscience of American scientists in the field.

I have in mind talking to Freund as president of the Academy to see whether they might wish to assume this as a serious undertaking.

DR. STEWART: Dr. Odegaard.

DR. ODEGAARD: Dr. Shannon, I think that's a very interesting suggestion. And my comment really is addressed to a query as to whether there is one step before that discussion begins. After all, the NIH is, so to speak, a collaborator with a variety of clinical investigators. Would it not be desirable to have before the American Academy and the procedure takes over for the broader discussion to have a proposal of some sort stemming from the

clinical investigators themselves as represented by NIH plus something or other, whatever that might happen to be, with a draft protocol and an input from the clinical investigators at the staff. Then, the surrounding context of this could be discussed in the larger framework you are talking about.

DR. SHANNON: We had those discussions with a group of mature people over a year ago. The draft proposal before you stems from our thoughtful consideration of their recommendations. So, what I suggest for the National Academy would in no way diminish our interest in your comments on this present proposal. I agree that there are certain things we should be doing within the context of our administrative responsibilities at the present time.

What I have in mind is more broadly to modify the social conscience of our investigators, and I feel that a mechanism such as the National Academy of Arts and Sciences is probably the most suitable way to achieve this.

DR. ODEGAARD: I think what I am really trying to do is protect NIH from being the sole and prime mover here as the fund granting agency, looking to the conditions of grant making. I know that is not the intent.

Maybe this is unnecessary, but my radar system tells me that this ought to be more than NIH initiating this in order to avoid potential conflict within the group of clinical investigators to the largest possible extent.

DR. SHANNON: There are five groups that one might discuss this with, and we would be quite willing to undertake it if that is your recommendation.

On the medical side, there is the Association of American Physicians, the Society for Clinical Investigation and--

DR. KENNEDY: American Federation.

DR. SHANNON: I was thinking more of the American College of Physicians as the third.

In the surgical area, there is the American Surgical Association, the senior group that relates in its sphere to the Association of American Physicians. Then, there is the American College of Surgeons.

I think it might be possible to discuss this matter with representatives from those five groups, which really encompass the bulk of the mature investigators. The American Federation for Clinical Research that Tom mentioned could be brought in, but there is some overlap with the Society for Clinical Investigation. Frankly, I would hope not to involve the AMA in this because their primary concern is the provision of services, and this would lead to undue complications.

DR. STEWART: May I suggest that at least my interpretation of the remarks is that we are really talking about two things:

We are talking about an eventual protocol which is sort of the guides that emerge from an interpretation of social conscience by those types of individuals and areas who are in tune with the social conscience.

And we are also talking then about a procedural document for our guidance in granting and other granting agencies which emanates from our present interpretation of the social conscience before such an examination and the development of such a protocol happens.

I suppose if one had his 'druthers,' he would wait for the protocol and then develop the procedural matters. But these have been discussed for such a time that it looks to me as if we can develop procedures now which step towards the eventual implementation of such a protocol, but will not be completely or at least would expect they would not be completely attune to the eventual protocol because we do not have that type of input into it.

Is this what I understand?

DR. ODEGAARD: In regard to that first step, administrative step, so to speak, I judge from Dr. Shannon's presentation that he is more worried about the independent judgment of the individual investigator controlling than he is about some of the fuzziness that may still exist with regard to the consent business.

If that be true, the Council might confine its activities at the moment to the procedureal step on the front of review by peers and not try to discourse on the whole thing.

Off the record.

(Discussion off the record.)

DR. ODEGAARD: So I would suggest that the first step be pretty limited in character and scope and you proceed with further discussions of these other clinical investigations.

DR. SHANNON: I doubt that the American Academy of Arts and Sciences would arrive at a basis for clinical protocol. They would be more likely to address themselves to the social conscience of physicians. I would agree with Bill that there are certain procedural things that can presently be done with propriety that would in no way jeopardize or prejudge what a more broadly oriented group might undertake.

DR. SMITH: Bill, there is one other element, and I would defer to Shirley Fisk on this and ask his opinion.

As you have presented it, Jim, the NIH is the "granting sponsoring" agency. The rest of those that are named are the investigator types.

Now, this is not mutually exclusive because the NIH advice is derived through study section and Council action, whereas, as you have pointed out, a definite administrative responsibility, they don't appear before Congress. You do appear before Congress. They don't appear before the Executive Branch. You are "the Executive Branch." So, in that sense, they still will be in there. And this is one of the pitfalls we got because even we as a Council constitute a not unbiased group because we represent--I don't want to pursue this too far, but in a way, we have some of the same built-in criticisms that we might have of an investigator himself.

But to get around to this, there is a group in the Armed Forces Epidemiological Board, for example, which has a minuscule volume of research compared to what is done here through the National Institutes of Health and Public Health Service and Bureau of State Services, but nevertheless has had a tremendous amount of experience, is confronted with the same sorts of problems--even more so. And I just wonder if Shirley would address himself to whether or not it might also be appropriate to think in terms of this because the DOD would cover, not only the AFEB, but ONR and the Air Force investigations.

I don't know whether this is going to complicate matters or make matters more difficult, but I would be very grateful if I could hear the reactions of both you and Shirley to this point.

DR. STEWART: Dr. Fisk.

DR. FISK: I think in terms of the matters that were brought forth by the last discussion, there are certainly areas in which human volunteers are used in experimental model. These are, as I say, "volunteers." These are fully cognizant of the hazards that--

You don't agree with this?

DR. SHANNON: No.

Off the record.

(Discussion off the record.)

DR. FISK: I think as procedures are now set up, at least in my time and knowledge of the procedures, there is a matter of consent. I am talking

in a narrow frame of reference, but I think as far as I have seen in this type of research, I believe that consent is given. The procedures are explained.

Again, perhaps I am dealing in a very narrow effort.

DR. SHANNON: I am talking from bitter experience.

DR. FISK: Off the record.

(Discussion off the record.)

DR. SMITH: Jim, I can only support Shirley. Times have changed, and I won't go into my own personal situation in this, but with something that was completely innocuous that couldn't help but do something to the benefit of the individual, it took us about three years before we were able to squirm that in and actually get that through. And now the situation is extremely different.

And I would just submit, Jim, that before a final decision is made that this also be considered because I do think that inevitably from this total pattern, and I think this Academy of Arts and Sciences sounds--I don't know enough about it--your presentation would seem to me to make this almost the ideal group to undertake it. But I do think it would be extremely desirable before a final decision is made on this to do some further consultation, because, believe me, things are very different now than they were at the end of World War II.

DR. SHANNON: I interpret Dr. Odegaard's comments as indicating that

before we impose any procedural limitations on a large number of scientists, there should be discussions within the groups who will bedirectly or indirectly affected. Wasn't that the sense?

DR. ODEGAARD: Off the record.

(Discussion off the record.)

DR. STEWART: What I would like to do is see if I can summarize now.

I think most of our discussion has really been trying to get ahold of the problem. And I think we have come up with a long-range pursuit which Dr. Shannon has suggested with the Academy of Arts and Sciences which is sort of the base that we are after. And I think I detect that the Council supports the idea of pursuing this.

Then, we have also carved out a more immedicate problem of what procedures do we do now. And I would, if it is all right with the Council, suggest that we now turn to these procedures. And that is really what this resolution is, in part, pursuing, I think, the avenue that was suggested by Dr. Odegaard that we try to develop these procedures to a point where we would like to have them discussed with those who are involved as Jim suggested.

Is this satisfactory?

I cut you off.

MR. WHALEY: I was about to say briefly it seems to me if we can address ourselves to the first step, we are not changing the law. In fact, I think there is probably a very good question as to the possibility of

diffusing this responsibility among a peer group if you get down to it. But we are doing something that we can do in the NIH. And that is the base judgment upon the validity of the research, on the use of peer groups for consent for an investigator to proceed.

And this is just like a hospital board considering problems of what does it do about sterilization. It works within the law, but it may have procedures that go beyond the law. And it doesn't change the pattern of society at all. But it does change its responsibility. And that really is what we have here.

DR. STEWART: Mr. Branscomb.

DR. BRANSCOMB: I wanted to comment on Mr. Wolfle's statement which applies here, too.

I see how you can leave out any reference to informed consent if you are dealing solely with a granting agency and had no other readers to have it in mind except the directive to the granting agency. But this document is going to get out to the public. It is going to be in the hands of many, many people. And if we issue it without any reference at all to the consent of the patient, I think what you are going to get is a howl from one ocean to the other on the ground that this proposal delivers the patients into the hands of a research institute, all of whom--the peers of the investigator--sharing to some extent the great primary concern with the achievement of knowledge and the values we have formed from possible experimentation.

Of course, we don't want to get into the question of trying to weigh at this top level the degree of consent or exactly who is capable of giving consent. My suggestion would be that the responsibility we place upon the peer group in sharing the decision would be to share in getting the appropriate wording that they shall share, not only in some judgment as to the benefits to be derived and the risks involved, but also the feasibility and validity of consent securing. Make that their responsibility, sharing that decision.

I think we have mentioned, then, we have protected ourselves from the misinterpretation that we are not concerned with the patient at all.

DR. SHANNON: May I point out a sentence that might be included in this? If you turn to the document--

DR. SMITH: Where are you?

DR. SHANNON: Page 2, the terminal sentence of the middle paragraph. We can type this up, and you can take a look at it later.

It is obvious that informed consent is an essential part of this general process--

DR. BRANSCOMB: I haven't found this.

DR. ODEGAARD: He is adding.

DR. SHANNON: Yes. Forget about the precise--

DR. FISK: Where are you adding that now?

DR. SHANNON: The last line of the second paragraph.

DR. PERKINS: Before the resolution?

DR. SHANNON: Yes.

In other words, I think the resolution should not dictate the mechanism,

but the forward should define the elements that should result in the apparatus. It is obvious that informed consent is an essential part of such a general process, and this should be obtained--

DR. BRANSCOMB: Wouldn't you have to put in something of "where feasible?"

DR. SHANNON: No. I would say only, "Informed consent." I think that if you start defining what is meant by "informed consent," you are lost. It is obvious that informed consent is an essential part of the general process, and this should be obtained so that the subject then becomes a co-investigator in the pursuit of new knowledge.

DR. ODEGAARD: Dr. Shannon or Dr. Stewart, you better tell me to leave the room because as I look at the words in the preamble here, I think we must bear in mind that all of us in this room start with certain kinds of assumptions. But when somebody outside this room reads these words, God help up.

"In this circumstance, the dominant professional interests involved shift from those of the physician to those of the scientist. Thus, the role of the patient becomes that of a means rather than an end."

My God, the mad scientist let loose, you see.

DR. SHANNON: This is precisely the comment, because we are as sensitive in this respect as an outsider.

DR. ODEGAARD: What I am leading up to, Dr. Shannon, is that what should be adopted here, it seems to me, is not the preamble, but let's just stick to the resolution.

DR. FISK: The last sentence, page 1, I don't see where you separate scientist and physician. They still can be one and the same.

DR. ODEGAARD: What I would like to propose, Dr. Shannon--every word here is charged as it is read in this larger environment--that we stick purely with the words of the resolution itself to cover the point that has been neglected. If at the moment, there is no primary issue being raised with regard to the consent doctrine, couldn't we simply state within the resolution, "Be it resolved, therefore, that the National Advisory Health Council believes that at some point in addition to the customary consent from the patient," and so on--that this second step be included and not get into the wording of the preamble which at least I feel is hazardous.

DR. BRANSCOMB: It could likely be extracted from the main document and discussed in isolation.

DR. ODEGAARD: All it has to be, really, is an allusion to the fact this is not customary; that we are focusing, then, by the review by peers.

DR. STEWART: You have the words a little further on in the resolution which talks about the protection of rights and welfare of the individual which is really what informed consent is all about, isn't it?

DR. WOLFLE: But if you want to put it in specifically, it can go down there--subject to review by his peers to assure an independent determination of the risk benefit of the scientific work involved and maximum protection of the rights and welfare of the individual or individuals involved, and then add, "And appropriateness of the procedures used to secure informed consent."

DR. BRANSCOMB: I like that.

DR. STEWART: I think that has it.

I wonder if we couldn't, Dr. Wolfle, get you to serve as chairman of a committee of a couple and mess up your lunch and draft something.

DR. WOLFLE: All right.

DR. STEWART: And we will get it typed as soon as you have it drafted. And then we would have it this afternoon for your consideration. Is this satisfactory?

DR. SHANNON: Iagree with Dr. Odegaard's point. It is well taken.

DR. STEWART: Is this satisfactory with the Council?

Dr. Odegaard, would you share with Dr. Wolfle that, and Mr. Branscomb, would you?

DR. BRANSCOMB: I am afraid I have a commitment for lunch if I can be excused from this.

DR. ODEGAARD: Dr. Wolfle will have it in a minute.

DR. STEWART: I am sure he will. If he will be done right away, that's fine.

DR. BRANSCOMB: On that ground, I will be ready to assist.

MR. DENISE: Speaking as a layman, is informed consent applicable to observation as well as experimentation?

I ask that because your resolution refers both to observation and the use of human beings.

DR. SHANNON: You will note, observation and experimentation drop out and the risk benefit of the scientific work is substituted. I suggest that "experimentation" be omitted. At NIH, we investigate patients, but we don't experiment with them. I think this slipped by me, since we never use the word "experimentation" in relation to humans. It is emotionally charged. "Investigation" is a broader word that encompasses experimentation without specifically-- Dael, would you substitute "investigation"?

DR. WOLFLE: There is one other word I want to add. And that is before "research", I suggest we say "clinical", because sociologists, anthropologists and educators also observe human beings.

DR. SHANNON: Yes.

DR. ENARSON: Mr. Chairman, may I comment?

I think there is more fundamental conflict in here. I think we are trapped in good part by the conventional ritual language of NIH. I refer specifically to the peer group.

I for one would not be content to rely upon peer group judgments entirely and exclusively for some of the reasons that Dr. Shannon indicated

and for some of the other reasons that I think are quite obvious.

It strikes me as perfectly clear and plain that the temptation that the individual investigator has to minimize the hazard to the patient is a temptation likely to be shared by his colleagues. So it seems to me that relying solely and exclusively on peer group judgments is not adequate.

May I follow that up briefly with an illustration?

We do have devices for getting at the conscience of the community in issues where you not only have science in abstraction, but you have the question of consent as a question of substantive as well as legal determination.

I think particularly of the very expensive kidney machine now in operation on the West Coast. I think it is very significant that we do not leave a peer group as the exclusive judgment as to who lives and who dies. For good cause, we incorporate the judgment of other people in the community.

And quite apart from public opinion and public reaction, just simply on the merits of the thing, I would like to see some procedure which insists that the peer group be defined as not exclusively clinical or medical, but defined more inclusively in terms of the total problem which embraces consent. That may be solely an individual point of view.

DR. STEWART: I think you have raised an important point.

Is there any discussion on the point that Dr. Enarson has raised?

MR. WHALEY: The point of operation within an institution?

DR. SHANNON: I would object to that. I know the work of the Seattle group. We have supported it for a number of years. I think the type of judgments that they reach are extraordinarily different than the type of judgments we are talking about here. They are deciding whether a person within the group should or should not live. And basically, what they are determining, having the capability of permitting a certain number to live, is whether or not the individual will be of benefit to or of detriment to his social unit. This has to do with the family stability, economic capability, intellectual capability of producing for the benefit of society, and things of that sort.

I think, to take that as an example, you unnecessarily burden a professional group which I think has shown itself over the years, when not involved emotionally with their own individual experiments, to be conservative, certainly highly moral, highly ethical, but nonetheless cognizant of the stakes. So I think to go beyond that would be to create an apparatus that would not be acceptable to the scientific community. However, that is less important, I think, than to create a mechanism that would hamper rather than benefit.

DR. ENARSON: Dr. Shannon, the peer group judgment as defined here is necessarily a scientific judgment. As I take it, we are dealing with

ticklish borderline situations in which the question of whether consent was in fact gained, the question of the degree of risk, is a factor.

DR. SHANNON: And I say that a nonprofessional can't contribute to that judgment.

DR. ENARSON: I challenge the implicit proposition that peer group judgments necessarily incorporate ethical and moral judgments as well.

DR. SHANNON: I would contest your attitude. We have seen this in a number of circumstances where peer groups were operational. They did not limit themselves to the technical aspects of the problem, nor indeed was that the purpose of their formation. However, they must have an understanding of the technicalities of the risk, as well as the possible benefits. Within these parameters, they arrive at a moral and ethical judgment as to whether such a thing is suitable or unsuitable.

DR. ENARSON: You are asserting, in effect, that men in the university communities whose lives are devoted to a systematic analysis of legal, moral, ethical issues have nothing to contribute to the process. And that strikes me as a highly dubious assumption.

DR. STEWART: Dr. Odegaard.

DR. ODEGAARD: I want to say the Seattle case is totally irrelevant here. That's a case of so many stations available and there being a substantially larger group of individuals. Obviously, what we are trying to do is increase the number of stations. But that has no bearing on this problem.

DR. ENARSON: It does, Charles, in the sense we are searching for a mechanism which will define in specific instances what is the conscience of the community.

DR. ODEGAARD: I simply say I think the crux of the case is that there is a fundamentally different element involved in the Seattle situation at the present writing. It is simply the absence of enough bills or enough machines or whatever you want to call it to go around for the number of people who could use them. The thing to do is try to increase those. But that is not really what I think is before us.

I would say, Harold, that we have lived with--and this is one reason I think we see all the clinical investigators involved--a tradition of professional men possessed of the clinical and specialized knowledge at the same time being sensitive to the moral implications of what they are doing. And I don't think you can put an outside policeman in here very effectively.

DR. STEWART: Are there other Council members who would like to speak to this point?

DR. PERKINS: You shouldn't hamstring the research. I am afraid in a procedure of that sort, it would hamstring it.

MR. WHALEY: Could you add one word to the last page. "The presence or absence and breadth of such a framework should be considered." This would keep you from getting two or three fellows that are intimately connected with the problem of making your peer group.

DR. STEWART: Did the Council hear that suggestion?

DR. BRANSCOMB: I don't know what it means. I would, therefore, be a little opposed to it. It introduces without saying so exactly this other element.

MR. WHALEY: Without defining "peer group" here, there is the possibility you might have three or four collaborators on a particular matter they are working on in which they are all dedicated. You would feel better about this peer group if you had someone who was dispassionate about it. So could you include the word "breadth" of the peer group and leave that to qualitative judgment again as to whether you are really doing it or not?

MR. DENISE: If the investigator is doing it, it wouldn't meet qualifications for the peer group, really.

DR. BRANSCOMB: The resolution calls for the approval of the procedure of review by peers by the institution. "An arrangement to provide for this review by peers of proposed clinical investigation should be clearly provided for in every institution where such work is conducted."

So I think you have got more than really an accidental group of three or four peers involved. You have the institution assuming responsibility for it. This is where I think this would hold true.

But I am concerned as we have it in here that the public understand that the consent of the patient is also part of this whole process.

DR. ENARSON: Are we dealing with essentially a public relations problem so that we are trying to put a fair face on things, or are we dealing with problems of substance?

DR. SHANNON: To my mind, we are dealing with problems of substance.

DR. ENARSON: Right. And I take it from your earlier comment, Dr. Shannon, there have been instances in your experience and rather serious instances where an individual investigator was carried away. And perhaps I misunderstood you in the implication of this.

DR. SHANNON: That is correct.

DR. ENARSON: I took it also to be true there are instances and might well be additional instances where the peer group judgment was also erroneous. Is that true or not?

DR. SHANNON: I think human nature has its frailties. In any series of judgments, by the law of small numbers probabilities, some are going to be wrong. This is true of the jury system or whatever. But I am concerned that we not develop an attitude which denies, in effect, that a well-constituted group of senior professionals can apply the necessary moral and ethical judgment to a procedure in which both the risk and the potential benefits are understood. That is my point.

DR. SMITH: Jim, some of the harshest actions I have seen have been taken by peers.

MR. DENISE: By medical peers?

DR. SMITH: Exactly. They see this really in terms of the Hippocratic oath plus.

I think your thought actually goes into the second part of this--further enunciation. But I just think that to try to get away from, you might say, the scientific conscience review of peers makes it completely unworkable. We couldn't manage.

DR. SHANNON: Of course, the other thing, Chuck, is my experience with nonprofessional people. They are more easily sold and more easily motivated to go along with the procedure.

DR. ENARSON: I am not aware that that suggestion has been made by anyone and surely not by me. My question was a very narrow one. And it is whether there might on occasion be utility in having somebody from outside a conventional peer group. And I think you have really answered my question. You are, in fact, dealing with a public relations problem.

In your judgment, if peer group judgments are made and if the consent of the patient is obtained, we have then the best of all possible worlds. This is really what you are saying.

DR. SHANNON: I am really convinced of that.

DR. STEWART: I think, Harold, the resolution as it now states this is saying that we are not defining peer group in here; we are really leaving it up to the institution to define what a peer group is. And your choice here is as to whether we define peer group or whether we do leave it up to the institution to define peer group.

DR. SMITH: And we are in just as big trouble if we try to define peer group as if we talk about informed consent. And either of those gets us into a morass in which we would have to have a resolution ten miles long and would confuse people more than ever.

DR. SHANNON: I think this really attempts to do two things.

It forces an institution to accept responsibility for the procedures that take place within it. And it outlines two important elements that should be considered in the discharge of their responsibility--informed consent and judgment by a peer group. We don't define what informed consent should cover. Nor do we define the formalities by which peer judgments should be determined, the consent of the peer group, or the mechanisms.

I can't emphasize how important it is for us not to intrude into how the university or hospital discharges responsibility, but only to outline the major elements to be satisfied.

DR. STEWART: Joe.

MR. MURTAUGH: Bill, I wanted to emphasize or restate what Dr. Shannon said, I guess.

The resolution was intended to achieve two very simple things.

One, to set forth the principle that the concerned investigator's judgment was not sufficient. And this, by the way, is a controversial principle. There will be investigators who will contest it.

Secondly, because of that fact, there must be a framework which submits the concerned investigator's judgment to review. And in the presence of such a framework must be a qualitative attribute of the project proposed for support.

TAB 68

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Statement by Director, National Institutes of Health
Public Health Service

on

1967 Appropriation Estimates

Mr. Chairman and Members of the Committee:

It is once again my happy duty to report to you on the progress of the NIH programs and to testify to the needs of these programs for the next fiscal year. As always, I welcome this opportunity to appear before you.

In my opening statement last year I discussed, in some detail, the directions in which biomedical research seems to be moving and the role which Federal support programs--and the NIH programs in particular--might most usefully play in the years immediately ahead. I described the growing importance to the understanding of disease

--- of comprehensive studies of human development,

--- of research in molecular biology, especially into the mechanics of genetics,

--- of a thorough exploration of environmental and behavioral factors in the cause of disease,

--- and of the application of the techniques and tools of the physical sciences and mathematics to the solution of biological problems.

These are long-term trends in medical research. What I said about them last year is equally true today--perhaps just a little more so.

As my views on the goals and future directions of the NIH programs are already on the record, I shall confine myself to a brief account of the present state of the NIH programs and to a summary of the 1967 budget request. I shall, of course, be glad to discuss in more detail any points which members of the Committee may wish to raise.

Each of the Institute Directors will report to you on the specific accomplishments in the various categorical areas. To illustrate the heartening progress made during the past year all along the frontier of the war against disease, I should like to mention a few examples of research achievements and of promising new projects.

As prevention is the only feasible 'cure' for many serious congenital anomalies and diseases, it is particularly important to develop better techniques for predicting under what conditions these defects are likely to occur. One such new technique is a blood test for identifying women who may be carriers of a gene causing progressive muscular dystrophy. This form of the disease, which accounts for two-thirds of all cases of muscular dystrophy, is inherited--half of the male children born to women who carry the gene will have the disease even though the mother shows no sign of it. The new blood test will identify 75 percent of such women. If the test is widely adopted--and, more importantly, if affected women heed its results--a large number of these tragic cases could be prevented.

The new blood test for carriers of progressive muscular dystrophy is only one of a steadily growing array of tests and procedures for detecting genetic defects that may be passed on by a parent to a child. There are now a score of inheritable errors in metabolism which can be identified in apparently healthy adults who are unwitting carriers. These include galactosemia; various blood abnormalities, such as certain types of anemias; a form of rickets that resists treatment with vitamin D; abnormal drug sensitivities; and, of course, the disease now widely known as PKU. Many of the abnormalities for which pre-natal tests are already available are fairly rare but this is no consolation to the family that is stricken by one of them.

These developments are beginning to make it possible for the medical profession to offer a kind of pre-marital counselling that could ultimately result in a sharp reduction in the incidence of a number of congenital abnormalities including some which result in severe--and tragic--mental retardation.

The medical profession has a moral obligation to warn prospective parents of the disabilities they may pass on to their children when this is known or readily determinable. The time has come when this responsibility must be taken seriously. Advances in medical research are making it possible for medical practioners to save the

lives of many children with a transmissible birth defect who, a decade or so ago, would have died before reaching child-bearing age. The effect--if I may put it bluntly, Mr. Chairman--is that we are gradually weakening our genetic inheritence. By our humanitarian interference with the operation of natural selection we are saving many lives but we are also to some extent degrading the health of the nation. Genetic counselling is thus becoming not merely a moral obligation of the medical profession but a serious social responsibility as well.

The prevention of the congenital abnormalities for which premarital or pre-conception tests are available is, of course, only possible if the affected couples do not have children. This is certainly not always a very happy solution.

It would be a much better solution if we could remedy such genetic defects. This is, as yet, but a distant hope. However, fundamental research in genetics is making progress on the problem of identifying which part of a gene is responsible for passing on certain characteristics to an off-spring and a beginning is being made on techniques for altering genetic traits. This very new field,

sometimes called "genetic engineering", presents a possible avenue towards the prevention of inherited diseases and disease-proneness about which only the most imaginative scientists dared to dream a few years ago.

The 1965 Nobel Prize in Medicine and Physiology was awarded to French scientists at the Pasteur Institute for their studies of gene regulation. Two of these three scientists have been NIH grantees for the past four years. One of these grantees, Dr. Jacques Monod, used the occasion to severely criticize the lack of support available in France for fundamental research, especially in relatively new fields which have not yet been recognized as separate disciplines by the highly conservative French universities. In a widely-quoted press interview he said: "If we have a debt, it is above all to the United States.....French research has benefited enormously from the American contribution." I would only add, Mr. Chairman, that medical science has also benefited enormously and that, in the long run, the health of the American people will benefit enormously from the trail-blazing work done by these French grantees.

There is a great deal of activity in the relatively new field of biomedical engineering. Grantees of the Heart Institute have invented two new pacemakers which are more efficient, more reliable and more convenient than the earlier battery-powered models. I have on my desk in Bethesda a prototype component of an implantable artificial heart developed,

with NIH support, by a collaborative project at Baylor and Rice Universities. Six new contracts have recently been awarded for research on artificial heart mechanisms. The National Institute of General Medical Sciences is supporting 67 biomedical engineering projects which include such new approaches as the use of ultrasonic techniques for medical diagnosis, the development of a combination television-camera and computer which can make and record laboratory observations, and the ingenious application of mathematical processes used by utility companies for the study of power transmission lines to the study of the human nervous system.

There have been a number of important advances in vaccine development. A live oral vaccine against adenovirus type 4, which has caused severe epidemics of respiratory disease in military training camps, has now been successfully tested in field trials. There is also a very promising new experimental vaccine against Mycoplasma pneumoniae, a primitive organism which is a major cause of a form of pneumonia among college students and military trainees. Good progress is being made in the development of an improved immunizing agent against tuberculosis.

Work on a vaccine against German measles has been stimulated by the funds which the Congress made available for this purpose in the 1966 appropriations. An intensive collaborative program has been launched in an effort to develop such a vaccine. Additional evidence of the viciousness and insidiousness of this disease--which most people regard as a relatively mild and routine childhood infection--has turned up during the past year.

A study of some of the 20,000 to 30,000 infants with birth defects resulting from the 1964 and 1965 rubella epidemics shows that German measles contracted by the mother during pregnancy can cause a number of birth defects that had not previously been associated with this disease--these are serious defects such as bone marrow lesions, anemia, hepatitis, and a severe hemorrhagic disease. It has also been found that an apparently normal infant who was exposed to maternal German measles early in pregnancy can shed the virus for as much as 18 months after birth thus spreading the infection to other pregnant women. A valuable tool in the battle against German measles is a much more rapid test for identifying those who have been exposed to German measles. It used to take two weeks to make this determination; the new test, which was developed at NIH with the cooperation of several outside scientists, does the job in 24 hours.

The significant contributions to the work on German measles made by Dr. John Sever of the Neurology Institute and Dr. Robert Huebner of the Allergy Institute is an example of the important role which NIH intramural scientists play in the nation's medical research effort. An interesting indication of the scope of the NIH contribution is shown by an analysis of the papers presented at the May 1965 meetings of the American Society for Clinical Investigation and the American Federation for Clinical Research at Atlantic City. These professional societies are very selective in accepting papers for presentation at their meetings—of a total of 881 papers submitted only 234 were accepted. It is significant, I think, that more than half of the papers submitted by members of the NIH staff

were accepted--the societies accepted a higher proportion of the papers submitted by NIH than any other major institution represented at these meetings. In fact, more NIH papers were presented at these meetings than those of any other institution. Of the 234 papers read, NIH scientists presented 26, or more than 10 percent.

As in previous years, the outstanding contributions made by the NIH intramural programs were again recognized by the selection of a number of NIH scientists for special honors and awards. I am happy to say that of the 27 members of the staff so honored two are women.

Dr. Rachel Larson, on the staff of the Dental Institute, was elected a Fellow of the American College of Dentists in recognition of her studies on the cause and prevention of dental caries.

Dr. Nina Starr Braunwald, Deputy Chief of Surgery in the Heart Institute, was named "Outstanding Woman in the Field of Medicine" for her pioneering work in open-heart surgery and her research on artificial heart valves. Her husband, Dr. Eugene Braunwald who is Chief of the Heart Institute's Cardiology Branch, was one of the recipients of the Arthur S. Flemming Award given to the ten outstanding young men in Government for achievements in science.

The U. S. Junior Chamber of Commerce selected Dr. Frank Rauscher of the Cancer Institute as one of the ten outstanding young men in the U.S.--in fields not limited to science—for his significant contribution to cancer research by isolating a virus that produces leukemia in mice.

The first recipient of the James Clarke White Award of the Association of Military Surgeons was Dr. Eugene Van Scott, Chief of the Cancer Institute's Dermatology Branch, for his contributions to the control of serious skin diseases.

International recognition of the achievements of NIH scientists is illustrated by the selection of Dr. Robert J. Huebner, of the Allergy Institute, by the famous Pasteur Institute of Paris for its annual Pasteur Award. The Italian 'Alessandro Pascoli Prize' was awarded to Dr. Walter E. Heston, of the Cancer Institute, who was the first to demonstrate the genetic nature of susceptibility to tumors in mice. The German 'Gerhard Domagk Prize' was awarded jointly to Dr. Dean Burk and Dr. Mark Woods, of the Cancer Institute, for their distinguished research in biochemistry.

If I may, I should like to submit a complete list of these awards for the record.

The budget estimates for the Institutes and Divisions of NIH total $1,302,764,000. Of this amount $71 million is for the three construction grant programs for which separate appropriations are provided. The request for the operating appropriations for NIH is therefore $1,231,764,000 which represents a net increase of nearly $93.4 million--or 8.2 percent--over the 1966 appropriations.

The largest single increase is for the new Regional Medical Program to combat heart disease, cancer and stroke and related diseases which the Congress authorized last September. The FY 1966 appropriation for this

program was $25 million. The budget request for FY 1967 is $45 million. There is a great deal of interest throughout the country in this new program and local planning is going forward at a rapid pace. We have been very fortunate in obtaining Dr. Robert Marston to join the NIH staff to head this program. Dr. Marston comes to us from the University of Mississippi where he was Vice-Chancelor and Dean of the School of Medicine. He is a Virginian by birth and is a graduate of the Virginia Military Institute and the Medical College of Virginia. He also has a Bachelor of Science degree from Oxford University which he attended as a Rhodes Scholar. Dr. Marston is Chairman of the Mississippi State Medical Education Board and, in addition to his many academic posts, he has had an active research career.

We are requesting $477.7 million for regular research project grants which is just over $20 million more than the 1966 appropriation. Of this amount, $19 million is needed to meet the increased costs of existing research projects which we have a moral commitment to continue. These are the so-called "non-competing continuations". The $141.4 million provided for competing projects constitutes an increase of $1.2 million over the 1966 level.

Increases totalling a little over $12 million are distributed among the various special research grant programs. Of this amount $6.5 million is for the General Research Support program. The addition of $2.5 million will bring the basic program of formula grants to medical and other health-related professional schools to a total of $41.7 million.

General Research Support awards to university departments will be increased from $5 million to $6 million and the new Health Sciences Advancement award, designed to stimulate the development of research capability in institutions which have lagged behind the mainstream of the biomedical research community, will be increased from $1 million to $4 million.

An additional $2 million is requested for the development of special animal resources, $2 million for the primate centers, and $1.5 million for the development of pharmacology and toxicology research resources.

The increase of $3.7 million requested for Fellowships is primarily intended for Research Career Development awards. These awards are making a significant contribution to the continued strengthening of our national capability to conduct sophisticated medical research. They are an important element in laying solid foundations for future research progress. I am convinced that it is most important to continue to expand this program at a modest but steady pace. An additional $6 million for training grants—representing an increase of about 3 percent--is needed to meet the normal rise in costs of these essential programs.

A substantial increase of $15 million is requested for Mental Health Staffing grants bringing the total budgeted for this program to just under $34 million. These grants are making a major contribution to improving the quality of care available to patients with mental disorders in every part of the United States.

The amount requested for the direct operations of NIH is $237.5 million which is $17.5 million more than the comparable amount available in FY 1966. Approximately $3.5 million of this increase is for mandatory items. This leaves some $14 million for a number of significant program developments. Of this amount more than $4 million is for the direct research activities of the Institutes. These increases will permit increased emphasis in surgery and cell biology in the Cancer Institute; fuller utilization of the anaerobic (oxygen-free) laboratory in the Heart Institute; and the strengthening of research programs in the Child Health Institute in reproductive biology, endocrinology and ecology in the behavioral research laboratories made available to the Child Health Institute by the National Naval Medical Center.

Increases totalling $2.2 million are provided for the collaborative programs. These funds will be used for such important research undertakings as the development of an improved artificial kidney in the Arthritis Institute and for developmental research and production of prototype rubella vaccines and for transplantation immunology and tissue-typing studies in the Allergy Institute.

Increases for the Office of International Research, which are included in the $14 million program increase for direct operations, include $2 million for the U.S.-Japan Cooperative Medical Science Program. As you know this program was initiated by President Johnson and Prime Minister Sato as a result of their meeting in January of last year.

Details of the program were worked out at a meeting in Tokyo of the American and Japanese Committees in April and at a joint conference in Hawaii last October. It was agreed that the program would be mainly focused on research on cholera, leprosy, tuberculosis, parasitic diseases, virus diseases and nutritional problems. Each country will finance the research of its own scientists. In addition to the funds requested for this program in the General Research and Services estimate, a number of related grant projects will be financed by the Allergy and the Arthritis Institutes. The total NIH contribution to this joint program is expected to be almost $9 million.

Although the increases over the current appropriations provided by these estimates are modest, the total request for $1.3 billion represents a very substantial national investment in biomedical research. The first budget request for which I testified after I became the Director of NIH in August 1955 was for $126 million for Fiscal Year 1957. The budget request to which I speak today is more than ten times that amount. With prudent management--and a measure of flexibility in the allocation of available funds--it will maintain the extensive NIH operating programs at satisfactorily productive levels and will enable us to move forward at a reasonable pace with the new Regional Medical Programs.

TAB 69

NIH INTERNATIONAL RESEARCH SUPPORT

Testimony for the Research and Technical Programs Subcommittee,
Committee on Government Operations, House of Representatives

The National Institutes of Health, through the Surgeon General of the Public Health Service, derives its legislative authority to participate in international activities from Section 308 of Public Law 86-610, the International Health Research Act of 1960. Under the provisions of this legislation, the Surgeon General may engage in international cooperation "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research and research training." In order to carry out its prescribed mission, NIH has used this authority to engage the unusual talents of some of the most outstanding scientists throughout the world on health-related projects of importance to the American people.

Testimony to this talent may be seen from the highly competitive selection process which we use. The procedure enables the best-qualified American scientists in a given field to judge the scientific merit of one application against another. Proposals passing the first screen are again judged by a second group of competent outstanding American advisers in terms of whether the work is likely to advance American medical knowledge of an important and priority nature. By the time the judgment is made in favor of an applicant from outside the United States, we may be assured

that the applicant is the most competent person to carry out the research in that scientific area. The recipients of support, because of their exceptional qualifications, are affiliated with outstanding centers of excellence throughout the world.

It may be appropriate at this point to examine the reasons why these American scientific advisers to the Public Health Service recommend the support of scientists in other countries.

Perhaps the most important reason is a recognition by the American scientific community of the interrelationship and interdependence between scientists at work in different countries.

A second important reason is a recognition of the unusual capabilities of the individual investigators. This uniqueness may involve personal talent or specialized education, training, or laboratory work which produces men of high scientific stature. It is through these men and their centers of scientific excellence that great achievements and advancement in science have been made abroad. Unusual or unique research complexes exist in certain countries. One such example is a laboratory of physical chemists and engineers in Holland capable of tackling certain biological aspects of the arteriosclerosis problem by using methods of the physical scientist. Other examples of unique capabilities include the huge electron microscope in Marseilles; a large and diverse group of immuno-chemists at the Pasteur Institute in Paris; a germ-free laboratory in Sweden; and a high altitude research laboratory in Peru. All represent remarkable opportunities for the conduct of research--and training of American

scientists--by the best minds in research, thus adding to our own fund of knowledge and experience.

A third reason for supporting research abroad is the frequent availability of unique population groups, with unusual genetic composition or variations in the incidence of disease. Studies performed in other countries have often shed important new light on cancer, heart disease, and other health problems of the American people.

A fourth reason is the necessity for conducting research on diseases which, though not found in the United States, are a continual threat to this country. The hazard grows as our personal interchange with other nations increases. Particularly, there exists a problem in the developing countries with which we have continual contact, but which lack the financial and other resources to do such research and yet possess the ecology in which the disease can be studied. Examples of this are schistosomiasis, which occurs even in Puerto Rico, and typhoid fever, a disease sometimes acquired overseas which must be treated in hospitals in this country. American physicians must also be required to protect our citizens going abroad with vaccines against such diseases as cholera and smallpox prevalent primarily abroad. Practical field tests of vaccines against these threatening diseases can only be conducted abroad where the incidence is great enough to give significant data. Often the research can best be conducted by a bi-national team with an institutional base in the United

States. Studies on a trachoma vaccine by Dr. J. C. Snyder of Harvard in Arabia and Dr. J. Thomas Grayston of the University of Washington in Taiwan are examples of this cooperative research, as are the studies by Dr. C. Henry Kempe of the University of Colorado on smallpox in Madras. One ordinarily thinks of trachoma as a blinding disease indigenous to Egypt and parts east. Actually, it is of serious concern to this country, being the most important threat to eyesight among our Indian population in the Southwest.

It should also be noted that awards to investigators abroad are used not only for research on diseases common in the United States, such as cancer, heart disease, etc., but also for research on diseases threatening this country and likely to be encountered by our military forces in South Vietnam, such as cholera, malaria, trachoma, dengue, smallpox, typhoid, leprosy, dysentery, schistosomiasis, and intestinal parasites.

Other reasons for the support of research abroad which are related to the NIH mission should be mentioned. These include the effect it has on augmenting our domestic manpower pool of scientists, the benefits of associating with outstanding scientific leaders abroad in other countries, and the promotion of American medical research techniques and methodology among peoples who can benefit from their use.

The Public Health Service started to support research in other countries in 1947 with five grants involving a total of $130,000. During the 1950's and early 1960's this support increased to a high point of

$15.5 million in fiscal year 1963. In 1960, when an appreciable increase in the number of foreign grants was noted, NIH began to review carefully the support being given to foreign investigators. An Office of International Research was established. Among its other functions, this Office examines the existing policies for supporting research in other countries, makes recommendations for administering such support in a reasonable manner, and maintains a continuing review of all Public Health Service research activities abroad. In addition, a small number of NIH scientific specialists were assigned in 1960 to our embassies abroad to assist in this review and to carry out a number of other important functions. Thus, the planned and systematic monitoring of international research activities began well before the ceilings on overseas grants were imposed by the Bureau of the Budget on May 29, 1963.

In 1960, in the interest of prudent administration of funds and without direction from outside, NIH began the development of policies and procedures designed to accomplish this purpose. Consequently, NIH was in a good position to participate in discussion with the Bureau of the Budget, the Office of Science and Technology, and the International Committee of the Federal Council of Science and Technology on how the essential integrity of the overseas operation could be maintained with minor impact on the substantive benefits of the domestic program. Policies evolved have been enumerated by Mr. Kelly.

During fiscal year 1965, the Public Health Service, including the National Institutes of Health, supported 833 research projects in 45 countries. Of the total amount of $12,170,000 awarded, approximately $1,400,000 is estimated to have been paid to American equipment manufacturers and $1,312,000 to have been financed by excess U.S.-owned foreign currency. This means that approximately $9,458,000 in U.S. dollars has in fact been expended abroad for urgent domestic reasons--a very small part (about three-quarters of a percent) of the U.S. dollar deficit. I should also like to point out that the $12,170,000 in awards for fiscal year 1965 represents a 16.4 percent decrease from the previous year's total award figure of $14,551,000, and a 21.4 percent drop from the comparable figure for 1963.

So, Mr. Chairman, I hope this brief review will demonstrate quite clearly that the policies governing PHS-NIH research abroad have been carefully planned to provide maximum program results with minimum dollar outflow. Working closely with responsible Administration groups, we have been quite conscious of the problems involved, have given them careful thought, and have taken constructive action. Finally, I would emphasize that support of research outside the United States is performed for the immediate benefit of our domestic programs as established by the basic statutes under which we operate, and has had the strong support of the appropriation committees of the Congress, who have maintained a continuing and quite specific audit on these activities.

TAB 70

NIH-OD-OPP - 2/14/66

THE REORGANIZATION OF THE PUBLIC HEALTH SERVICE

SOME RELEVANT CONSIDERATIONS

The Process of Change

The Public Health Service today comprises a diverse and complex set of programs addressed to the solution of national health problems through short- and long-range efforts and to the discharge of certain direct health functions. The total annual funding amounts to $2.4 billion (FY 1966). This is an increase of three-fold over 1960 when the last reorganization study of the Public Health Service was carried out. Legislation passed during this period, particularly in the last year, has broadened the scope of Federal health functions and shifted the character and emphasis of PHS activities. This process of change plus the advantage of 1966 viewpoints over those of 1960 provides the setting for a new formulation of the functions of the PHS.

In reaching for this new formulation it seems most important to set forth at the beginning certain basic considerations. These relate to (a) the historical forces which shaped current developments and will exert influence in the future, (b) the basic problem of relating research and science functions, (c) the attributes of organizational strength, and (d) essential components of the Federal health function. These matters are of such a fundamental nature that they must shape organization rather than be subject to it.

A. THE FORCES AT WORK

The postwar development of PHS programs has been strongly influenced by three broad sets of circumstances. In a very real sense, these are of the order of historical forces. They have shaped the past and immediate evolution of PHS programs; and their modification, in the context of further social, economic, and political advances, will significantly affect the future. These circumstances are (a) the thrust of science and the Federal role, (b) the Federal involvement in the delivery of health services, and (c) the development of health functions outside PHS.

1. The Thrust of Science and the Federal Role

The array of legislative acts at the end of the 1940's establishing the several categorical Institutes of NIH represented the Nation's decision to bring under control the major diseases and causes of death. The initiation of these programs was complicated by the inadequacy of basic biomedical knowledge of these diseases and the underlying biological phenomena. Thus it was clear that the attainment of an acceptable degree of control capability was crucially dependent upon the advance of science and the resources directed toward that end. This limitation was made clear in both the Executive and Legislative Branches of the Federal Government in the process of program and budget development by both official and private persons. Thus, the major postwar effort in the categorical disease programs has been directed toward overcoming this basic deficiency in knowledge.

The Growth of Research and Development

This course of events has taken place in a setting in which science, research, and technological development have emerged as a major instrument for the achievement of social goals and the furtherance of national prestige and prowess. Thus the past twenty years have seen the application of increasing Federal funds and greater portions of the Gross National Product to research and development activities.

The University Role

An essential concomitant of this basic trend has been the expansion of the research and graduate education functions of universities as major contributors to the advance of basic knowledge and the locale for the training of scientists, engineers, and other professionals. Research has now emerged as a distinct and substantive function in all major academic institutions. The problems of encompassing, administering, and supporting this mounting scientific activity have, during this period, become a major preoccupation of these institutions.

The Dependence Upon Federal Funds.

A salient characteristic of this postwar growth of science and the involvement of academic institutions is its vital dependence upon the flow of Federal funds and the programs, policies, and fortunes of the several Federal agencies involved. The total flow of Federal funds into colleges and universities for the support of research now (FY 1965) exceeds $1.0 billion; and the Federal expenditure for all academic purposes--research, training, and construction--is in excess of $3.0 billion.

The Mission Orientation

Despite the magnitude of the Federal expenditure in academic institutions, only a very small amount is expended with the primary purpose of supporting academic functions as such. By far the larger portion of this Federal expenditure is a consequence of the appropriation of Federal funds for major national purposes such as Defense, Space, Atomic Energy, etc., the accomplishment of which, as in the health field, requires broad support of basic research and the expansion of scientific resources. Only 14 percent of the $1 billion Federal funds spent for the support of research in academic institutions comes from the non-mission oriented programs of the National Science Foundation and the Office of Education. The remainder, 86 percent, comes from mission-oriented agencies, of which the NIH component, 36 percent, is the largest. Thus, the growth of science and the support of the requisite academic environment in the United States is critically dependent upon mission-oriented Federal programs, and the stability, cohesiveness, and perception with which these programs are administered. In this respect it is important to emphasize that in the aggregate, NIH programs in research and training are the prime support for a major segment of science. This is a vital support function which is indeed a subject of policy and program action as such.

Throughout this period, there has been a substantial national consensus on the Federal role in the support of science and the expenditure of Federal funds in academic institutions for science and related purposes. Broad national aspirations vitally related to the stream

of science and academic activity, rather than organization, personalities, or artful devices, have been the primary basis of NIH development in the postwar scene.

2. Federal Involvement in the Delivery of Health Services

The national setting for the development of Federal activity relating to health services in the postwar period was in considerable contrast to that existing in relation to science.

Minimal Role of the Federal Government.

In the first place, the role and function of the Federal Government in respect to health services have been essentially minimal. While Federal expenditures account for two-thirds of the national expenditure of $1.8 billion for medical research in 1965, the Federal portion of the total national expenditure of $35 billion for health purposes (excluding research) is only $5 billion, or 14 percent. These latter Federal expenditures are basically directed toward:

a. Health services for Federal beneficiaries (military, veteran, Indians, American seamen, etc.).

b. Discharge of Federal sanitation functions (foreign quarantine, regulation of interstate commerce, shell fish sanitation, etc.).

c. Assistance to States and communities through grants in support of public health functions, professional and technical assistance, demonstrations, and training.

d. The quantitative enlargement of health facilities and professional resources through grants in support of construction and training.

e. Health intelligence, education, and studies.

The Lack of Consensus

For the most part this Federal effort in respect to health services has not involved any direct penetration into critical problems surrounding the actual delivery of personal health services, the quality and cost of medical services, or the economic and sociological aspects of medical care. There has been no national consensus concerning the role of the Federal Government in these areas such as existed for medical research. Instead, there have been substantial bodies of opinion that rejected all government efforts in these directions, giving rise to prolonged and bitter controversy. Consequently, the primary issues in this area are not those relating to money which can be dealt with by budgets and appropriation committees, but legislative and national policy questions of the highest political order. As a technical agency, the Public Health Service has remained on the perimeter of these struggles. For its programs in the health services area, this has been a posture of safety, but a considerable restraint on their character, scope, and growth.

The Beginning of Change

The circumstances which engendered this course of events are now changing. There is growing public awareness of the advance of scientific

and technological capability in health and medicine and the existence of substantial differentials in the quality of medical care available throughout the Nation. The increase in national economic capability, coupled with a heightened sense of social action, has generated a growing expectation that important human wants and needs will be fulfilled. There is a growing national opinion that the critical problems of the availability, cost, and quality of medical care can be resolved through various forms of national action. The passage of such legislation as the Health Professional Educational Assistance Act, Medicare, Regional Medical Programs, and Mental Health Staffing is concrete, current evidence of this change.

The Shift in the Center of Action

The center of Federal action in the health service scene is therefore in the process of transition. Traditional forms of public health action and its State and local governmental mechanisms are giving way to new conditions of medical care and new structures and designs for health services at the community level. This is a beginning. The severe constraints under which Federal programs in the area of health services developed are just beginning to lift. In many respects these programs are now at a transitory juncture comparable to that of the federally supported medical research in the latter half of the 1940's, when the center of gravity shifted from direct Federal research operations to support of the national scientific community.

3. Development of Health Functions Outside PHS

Out of the vigorous growth of the national economy in the postwar period, another major transition affecting the health sciences took place. This was the shift of national concern in the area of domestic affairs from the depression-born problems of gaining a livelihood to the needs for advancing the quality of living and extending the benefits of the Nation's economy to all segments of American society. A consequence has been to envelop health objectives within other national programs aimed at broader social goals. These changes are illustrated by the initiation of national action directed towards the problems of Appalachia, the elimination of poverty, the problems of the aged, and the expansion of health related activities of the Childrens Bureau, the Welfare Administration, and the Office of Vocational Rehabilitation. A further aspect of this change has been the growing emphasis upon strong regulatory action reflected in the Food and Drug amendments and the controversy over administration of air and water pollution programs.

The establishment of new social goals has presented complex qualitative questions concerning the Federal role in health matters. The traditional concepts of Federal-state relationships have been greatly strained, thrusting to the fore new considerations concerning the scope, limits, and program avenues of Federal action. A shift in the professional-political interface in health matters has been the result. The major determinants of action in the health area have

moved upward to broader political considerations on the one hand and downward to more complex technical and scientific considerations on the other. Without question these developments have generated stresses and differences within PHS which no amount of equalizing efforts could correct because they were not managerial in origin.

B. RESEARCH VERSUS SERVICE

Beyond the influence of the broad course of national events, there is another matter which contributes to the basic immiscibility of activities centered upon research and science and those centered upon care and service.

1. The Short- and Long-Range Approaches

In the long view, the form and matter of any arrangements to deal with the delivery of health services and the character of medical care must be considered as temporary and mutable. The advance of knowledge, the evolution of technology, and economic growth are bound to transform the conditions upon which current health action is based. The certainty of this process of change is, indeed, a principal impetus to sustaining and advancing our capability in the health sciences. This effort and its long-range motivation must always seem in conflict with the difficult, complex, and necessary effort to deal with current problems with current means. In a very real sense, such conflict within an organization responsible for both long-and short-term goals carries the danger that the critical urgencies of the moment will prevail over the long-term needs.

2. The Accommodation to This Difference

In several European countries (The United Kingdom, Sweden, France), the complete separation of research and service into different departments has been chosen as the solution to this problem. Such departmental division would appear extreme and unwise in the United States, where the principal support of science derives from mission agencies. However, the inherent problems of this relationship and the potential danger to the vital long-range considerations mount substantially as the science fucntions are divided and distributed downward through the several levels of organization. The clear implication is that the programs in support of science and its resources should be maintained as a cohesive whole at the highest organizational level compatible with the general departmental framework.

C. THE ATTRIBUTES OF STRENGTH

Beyond the broad external forces that have influenced the development of PHS programs in the postwar period, there are considerations relating to the essential conditions of strength in the conduct of Federal programs. These have critical bearing upon organizational design. Thus the components of an organization, individually, should reflect or encompass:

1. A discrete, substantive area of social action and need which is innate to society as a whole, apart from government business as such (e.g., conduct of research or delivery of health services).

2. An important set of national objectives in each of the discrete areas of action, the attainment of which is a valid and desirable basis for public action.
3. A meaningful set of functions to be performed in respect thereto--functions comprising a cohesive whole, derived from legislative and executive agreement, and broadly recognized and understood.
4. A set of basic concepts, values, and principles relating to public policy which pervade program operations and decision-making, as essential to maintaining excellence and inducing high achievement on the part of the organization.
5. Intelligent, cohesive direction endowed with the requisite access to authority to relate action to need within broad Executive and Departmental goals.

While these activities are necessarily stated in general terms, they each identify an attribute which, to the extent that it is embodied in an organizational plan, will substantially determine the quality and vigor of a Federal operation.

D. THE INTEGRAL COMPONENTS OF THE PUBLIC HEALTH SERVICE

With a view of the forces at work and the general specification of the attributes of strength as background, the problem of formulating the functions of the PHS can be approached. These functions are of two levels:

First, a set of discrete areas of social need of primary PHS concern:

1. National Health Leadership. A dominant function of the PHS must be to discern the nature of forces bearing upon health and to influence the process of change to attain the best for the national health condition. Thus a vital role of the PHS is to influence the process of change in the national health scene. The ultimate focus of this function must be located in the Surgeon General. In order to discharge such leadership, the Surgeon General must be supported by an analytical group which can constitute the intellectual cutting edge of thought, innovation, and design for the further evolution of the national health condition. By this means, PHS can exert influence over a wide range of Federal health activities whether directly administered by the Service or not. In relation to other Federal health activities, the PHS should be in the vanguard in respect to the design of health arrangements, the determination of standards, and the source of innovation in extending new knowledge to practice. The Office of the Surgeon General, in respect to other components of PHS, should exercise a forward-looking and broad policy development and coordination function. Its concern with the day-to-day operating problems of the bureaus and other management detail should diminish.

2. The Community Health Structure. The center of national health action now lies in the structure, relationships and functioning

of the system of health and medical care services and resources at the community level. Here the major problem areas are (a) the availability and accessibility of health services involving the quantitative needs for facilities and resources and their organization and relationships, (b) the cost of health services and the complex economic questions surrounding the production, utilization and financing of health care, (c) the quality of health services, which presents some of the most complex and controversial issues of the present day health scene, (d) the motivational and behavioral obstacles that intervene in achieving the maximum benefit in the population as a whole from present day medical and health capability. These problems are closely interrelated. Thus the national effort toward their solution should be pursued as an integrated, cohesive whole.

3. The Prevention and Control of Health Hazards. Beyond the problems associated with the quantitative and qualitative improvement of health services generally lies the changing needs for special national action directed toward control and prevention of specific disease or health problems. In the past the communicable diseases such as VD and TB were the center of attention. Now the chronic diseases, the problems of particular population groups such as the aged, children, the

mentally retarded, and the control of environmental health hazards have moved to the forefront for special concern. This process of selecting major problems for special national action is likely to continue as an important facet of the Federal health function. The areas for such individual attention will change as new problems emerge and the urgency of the older problems diminish through the success of special efforts and the growing capability of general health services. Thus clear provision for the design of programs with specific goals to operate within limited time periods and for periodic regrouping of these program efforts should characterize this functional area.

4. The Professional Work Force. The development of the professional and technical work force for personal and public health services is emerging as a discrete national function, with a need for major innovation to meet problems arising in the community setting. The center of concern in this area is the educational process. In addition to effort directed towards enlarging the quantity, enhancing the quality of health manpower, new concepts of the character and utilization of the professional and technical manpower resources required for community health services should be evolved. The functions here would include analysis of the the professional work force in terms of the character and distribution of the manpower involved; further development of the

professional work force for health services; expansion of institutions concerned with the production of medical and health-related personnel; and the conduct of programs to enhance the educational process for health manpower, to provide support for individual students as well as the process, and to engage in the advance of educational innovation and coordination.

5. The Scientific Base. A necessary component of Federal health action is to foster the scientific base and the related resources for the development of new knowledge and technological capability requisite to an understanding and modification of the biological, behavioral, and environmental conditions of health and disease. Programs in this area would encompass the improvement of the physical resources for scientific activity, the support of research in the biomedical sciences at both applied and basic levels, career development of scientific manpower, the advancement of institutional capability for research and graduate education in the sciences related to health and medicine, and the support of technological and engineering development and the purposeful exploitation of research findings. The principal relationships of this area of activity would be with the universities, the research and graduate education function of professional health schools, and other institutions devoted to research and the advance of science in areas related to health.

The scope of this concern with science requires close relationships with the Office of Education, the National Science Foundation, and other agencies concerned with science and graduate education.

Second, a group of supportive and ancillary functions:

1. Health Intelligence. Intelligence relating to the incidence and prevalence of disease, insight into the dynamics of natality, and mortality, and the continuous surveillance of environmental health hazards are essential to the discerning of health trends and the prompt identification and definition of health problems. Sophisticated capability to relate changing demographic and disease phenomena and their economic and social substrates to national health planning and evaluation is a vital part of a national health program.

2. Health Communication and Information. Concern with the communication of information in health to the lay public, the practicing health community, and within the medical and related sciences plus the capability to store and retrieve such knowledge is an integral supportive element of the national health function. The relevant PHS activities in this area need to be regrouped to provide for greater unity and force in the area of health communication.

3. Ancillary Activities. By law and executive assignment, PHS is involved in administering health services for certain Federal beneficiaries, conducting the Indian health program, and providing

technical services in a variety of areas. For the most part these activities are ancillary to, and apart from, the major functions of PHS. To a great extent, their eventual disposition must be resolved in political terms. As long as they remain with the Service, however, they should reflect the highest standards and be conducted in a way that makes them a useful resource in the conduct of other PHS programs.

This identification of the basic PHS function provides a framework of essential elements for grouping into an effective organizational structure. Such a grouping should reflect the following qualities:

...Each component should have a definable mission understandable in itself and representing a real area of social need and action.

...In each area it should be possible to engender a cohesive set of objectives, provide for clear, comprehensive leadership, and differentiate the resources, mechanisms, and areas of action involved.

...There should be a conceptually compatible and complementary operating relationship among the basic components.

This view of the essential components of the Service does not provide for environmental health activities as a discrete function. Circumstances have changed significantly since 1960 when the Study Group on the Mission and Organization of PHS recommended the establishment of a Bureau of Environmental Health. Legislation has now placed

water pollution control activities at the Departmental level. Air pollution control functions may soon follow. Both these areas seem, in the long run, to be more a part of broader social problems, such as water resources and the conditions of urban living, rather than a health matter per se. Thus the further evolution of these programs, and indeed of other areas of environmental control, may well take place outside the Service and the Department. Thus the environmental health functions that remain with PHS will probably be those that, on the one hand, relate to the advancement of basic science and, on the other, can be encompassed within the framework of community health services and health agency activity.

TAB 71

CONFERENCE ON THE GROWING CRISIS IN MEDICAL SERVICES
AND MEDICAL EDUCATION

Ft. Lauderdale, Florida, February 20-25, 1966

Notes for Dr. Shannon's participation in the panel entitled
"GOVERNMENTAL ACTIONS ACCELERATING THE CRISIS"

1. <u>The nature of the governmental action affecting medical services and medical education.</u>

The title of the panel's area of discussion would seem to indicate that government, particularly the Federal Government, has unwittingly taken actions, the consequence of which are to accelerate the development of a crisis in the area of medical services and medical education. While there has been, indeed, a great deal of governmental action, the crisis that is emerging before us in the area of medical service and medical education is not a "crisis of calamity" generating chaos and despair, but rather a "crisis of opportunity" in terms of the promise that current national efforts have for overcoming major deficiencies in the character of medical services and thus the health condition of the Nation. Thus governmental action should not be viewed as the instrument of disorder in the medical services scene, but rather the effective expression of social recognition of the need and will for change in the health circumstances of the people.

The governmental actions of promise are epitomized by the passage of the following legislation:

1. The Health Professions Educational Assistance Act to enlarge the training capability of the Nation for the health professions.
2. The Social Security Amendments for the Medicare program which, for the first time, provide a framework of solution for the problem of financing medical care and health services for the aged.
3. The Heart Disease, Cancer and Stroke amendments providing for the establishment of Regional Medical Programs to bring about an effective relationship between the centers of scientific and academic medicine and the framework of community health services.

This legislative achievement has been built upon the broad postwar expansion of the Federal support of medical research and the efforts directed towards enlarging the health facility resources of the Nation through such programs as the Hill-Burton Hospital Construction Program. Thus in the postwar period, governmental action has brought clearly into focus two critical areas of need in the health scene: One, the necessity to overcome the financial impediment which has stood in the way of access to adequate medical care for large portions of the population, principally the aged. Second, the need to diminish the great disparity between the quality and character of medical services available in the university medical centers of the Nation and the level of care available in the generality of community health services.

The consequences of actions directed towards these ends is to reveal in clear terms, and in a manner that will sharpen the corrective action, the truly inadequate nature of our present health services capability when artificial restraints are removed from the scene. Thus the net consequence of the recent national action as represented by legislation passed dealing with health in the last Congress is to establish a growing national consensus concerning the need to act nationally, and in a more comprehensive manner, to remove the remaining barriers to adequate health services for the Nation. This emerging national consensus, in many respects, is a parallel to the national consensus relating to the Federal support of university research which emerged shortly after the end of World War II.

2. Regional Medical Programs

Because the National Institutes of Health has been assigned administrative responsibility for the development of Regional Medical Programs resulting from the Heart Disease, Cancer and Stroke amendments of 1965, it is useful to explore some of the potentialities which this program presents. In the first place the objective of this program is to diminish the differential between the quality of medicine available in our scientific and academic centers and that generally available at the community level in the Nation. In general this will be accomplished by providing for direct linkage between these centers of medical capability and the community framework of services. This direct linkage is the

essence of the regional medical program concept. In a very real sense this program contemplates moving the interface between academic and community medicine from the university medical center, where it now exists, outward to the major community hospitals of the country. This movement will be accomplished by the staffing of specialized diagnostic and treatment units in the community hospitals, by the development of programs of continuing education, by exchanges of professional personnel and by expanding the use of community hospitals as a setting for undergraduate medical education. This program has great potential for accelerating the flow and mking more broadly available the new knowledge and technology emerging in the medical scene. It will also serve as an effective instrument for more formal and durable programs of continuing education and contribute to the basic education of health manpower. In these terms this program will increase our capability for training and education, will provide for maintaining a high level of professional skill within the community setting, and contribute to superior health services.

3. The crisis in medical education and health services frequently is formulated in terms of growing disparity between the requirements for health services and the number and character of physicians being trained in the country. The discussion of numbers is not always a contributory or useful engagement. However, there is one aspect of this problem of numbers which has been of passing concern because of the national policy

considerations involved. The Health Professions Educational Assistance Act, centered upon increasing our capability for training of physicians, has had its basic dimensions derived from the implicit decision that it would not be in the national interest to allow the ratio of physicians to the general population to decline below the level existing at the time this legislation was formulated. The net effect of this implicit decision is to establish a set of construction requirements which in reality will mean that the places available in medical schools will occupy a declining position in respect to the proportion of the college age population which previously had moved into medicine. In other words, I think that the wiser national decision would have been to design the dimensions of our medical schoolsconstruction program on the basis of maintaining medical school capability at a level which assured at least a constant proportion of the college-age population entering medical school. Indeed, we might have considered extending Keynsian concepts to this problem by attempting to increase the proportion entering medical school during the period of the bulge in college-age population resulting from the postwar bumper baby crop in the anticipation that the proportion may decline in leandr periods.

Another matter that is of considerable concern to me is the significant number of individuals represented by that proportion of medical school applicants who are not accepted for admission. These individuals represent persons with a definite inclination toward health and medicine.

To the extent to which the closing of medical school doors to them directs them to other fields then we have lost a substantial resource to the health field. Maybe our discussion concerning the manner in which the physicians function might be subdivided would enable us to capitalize on what appears to be now lost talent.

4. In considering the manner in which we must distribute our efforts to overcome the many problems encompassed under the designation "The crisis in medical education and medical services," these kinds of questions come immediately to the fore; the manner in which we approach answers to these questions can, I think, guide us towards a more useful distribution of the national effort:

1. Can we significantly change the volume of morbidity and mortality in the Nation?
2. Can we significantly change the character and volume of formal health services which are either needed or sought by the people of the Nation?
3. Can we significantly change the flow of manpower into the health field?
4. Can we significantly change the total requirements for and the functional distribution of, and thus our educational framework, for health manpower?

In seeking the answers to these questions a productive resolution of the crisis may emerge.

TAB 72

OUTLINE FOR DR. SEADDON'S PRESENTATION BEFORE
MEDICAL INTERSOCIETY COUNCIL
March 17, 1966

I. Recent Developments and Present Status of NIH Programs

A. Postwar Growth

Utilize chart showing the four postwar stages of NIH development with comment aimed at setting background for areas of new policy and program evolution outlined below.

B. Present Organization Budget and Functions

Utilize chart showing NIH organization in proportion to budget showing relative distribution of functions by program.

II. Major Areas of Further Program and Policy Evolution

A. Strengthening the Framework and Resources for Medical Research

1. A formula for stability of support, the concept of the 15% rate of growth; the balance between project and general support.

2. Expansion of resources. Effort to develop greater institutional capability for biomedical science; the evolution of a broader geographical dispersion of broadly based centers of excellence in the medical sciences; career stability for medical investigators and educators.

3. The development of graduate education in the biomedical sciences.
4. The development of planning, analytical and evaluation capability within institutions as a basis for this further evolution.

B. Stimulation of new areas of scientific inquiry and technical development

1. Develop new institutional forms for areas of science incapable of development within current departmental framework
   a. Pharmacology-Toxicology
   b. Dental Sciences
   c. Aging
   d. Developmental Sciences
   e. Behavioral Sciences
2. Biomedical Engineering and Development
   a. Computer Sciences and automation
   b. Artificial organs
   c. Vaccine development
3. New insight into disease phenomena as a basis of prevention, control and future laboratory and clinical investigation
   a. Increasing cancer morbidity
   b. Diet - atherosclerosis
   c. Mental retardation and perinatal events

C. Acceleration of the Flow of Knowledge and the Quality of Medicine

1. New social purpose for university medical centers
2. Development of more diversified but better integrated systems of medical and health service
3. Development of more systematic continuing medical education
4. The relationship between the advance of medical science and the advance of medical practice
5. The role of Regional Medical Programs

TAB 73

Laboratory Management
April, 1966

NIH Director Views the Development of Molecular Biology

Photo courtesy NIH

Dr. James A. Shannon, Director, National Institutes of Health, does not view education as a formal process that ends with the acquisition of the PhD.

Q– *Dr. Shannon, would you say that today's level of research regarding the human body and its functioning is adequate?*

A– Even today there are many areas of science that can contribute greatly to human welfare, but are not being pursued with vigor. This is particularly true of the behavioral sciences, the very broad areas of biological development, and many areas of chemistry, physics, and mathematics, leading to the scarcely begun modeling of biological systems.

Recently Dr. Haworth (NSF) said, "We are now immersed in the fourth biological revolution . . . (the) molecular or genetic revolution. . . ." Would you care to comment on this?

The progress of the biological sciences that Dr. Haworth is speaking of first started with the response of the organism, man, as a whole; for example, his response to cold as the result of a general sensory input into the physiological system. Then investigators moved into the function of the individual organs or component parts of the total system in terms of characteristics and capabilities. From this point they proceeded to study the cells that composed the organs and attempted to determine the specific functions for particular cells with specific limitations and specific capabilities.

For example, the kidney, which is composed of about 2,000,000 nephrons, has organs within organs. These nephrons are individual units that filter the blood and then operate biochemically on the filtrate as it courses down the tubule and comes out as urine. Thus it is possible to visualize the nephron as the primary organ in the human kidney. The same thing is true for the liver, or any of the other organs and the specific cells that compose them.

This type of analysis is characteristic of a good deal of biomedical research of the 50's. The attempt to rationalize problems of heredity beginning with Mendel's time found evidence pointing to certain entities within the nucleus or within the protoplasm whose specific proper-

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today actually initiated their work at about that time.

With the techniques we now possess for the formation of polynucleotides and the synthesis of proteins, is it not possible now to forge ahead rapidly in producing new mutations, without waiting for the natural occurrences?

Regardless of techniques, this is slow progress; and however dramatic, it will not be a rapid move. The thing that makes it appear rapid is that this area of science is now at a critical point where individual contributions can have a very broad impact. This gives one the sensation of rapid movement. But if you go back into the historical development of any of these you will find that it has occurred over a very substantial span of years.

Would you say that the NIH under your direction has for the past several years been placing greater emphasis on basic research?

NIH has always placed great emphasis on basic research. The only thing we have done is respond to the pressure of very practical-minded people who want results. If they are sick they want cures; or they want removal from the worry or hazard of disease.

The entire apparatus of NIH has been very effective in convincing both the Congress and the people that over the long haul they must support a very broad endeavor at a quite fundamental level, because the knowledge available for rapid application is not adequate to assure the desired results. I don't think that we — and when I say "we" I am speaking on behalf of top management here — take any great pride in being peculiarly perceptive of this. We have just been prudent administrators, and we haven't promised what we cannot deliver.

Would you say there is a growing recognition of the emphasis that has necessarily been placed in the basic research area of chemistry over these years?

The biological sciences are now in a position, as a result of work done over the past 10 or 15 years, to put to good use much of the chemical information that has been accrued and is accruing. This is aided in no small way by improvements in instruments for measurement.

During the latter part of the 20's some departments of biochemistry began to apply principles of physical chemistry that were related to gaseous exchange, maintenance of hydrogen ion concentration, and so on. But the bulk of the work was not very sophisticated. Today, not because of any rapid change, but because of a whole series of successive steps, the people in biochemistry departments can deal with certain problems of biochemistry with a precision with which an organic chemist deals with his studies of synthetic organic reactions. What we have experienced is a maturing of biology and physics, chemistry and mathematics. This has been a natural evolution. Now, you ascribe it to us probably because we support most of it. But that is less because we want to support it than because of our very excellent advisory and examination techniques. These permit us to express support, through our grants, for what is good, significant, and progressive.

The Westheimer report has brought out that the NIH is the largest supporter of chemistry in 125 chemistry departments of universities. I take it from what you are saying that this has been an evolutionary process on your part.

That's right. This has been because chemistry investigations have a great deal to contribute.

With the leaders we have today right on this campus who are forging ahead in molecular biology, isn't there a need to upscale the volume of work that can be done?

Let me put it this way: It would be nice to have the money to do it, but there are restraints, such as available funds. As far as we are concerned, we are one element of the Federal establishment, and it would be silly for me to say we cannot run a good program with the money available to us. It would be equally silly for me to say we could not run a better program with more money. So we do the best we can with the funds we do receive.

Isn't part of the need in the training field? There was a recommendation made recently for a university, I believe.

I have always said that I would agree to let them start a very small, pre-doctorate program on an experimental basis — with no commitments beyond that. I know we have a great deal to contribute in training the post-doctorate. This might well be the most important role this institution could play, not so much in the preparation of the new PhD, but in picking him up from the university at that level and giving him a broad experience.

I do not view education as a formal process that ends with the aquisition of the PhD. With the movement of science today, the bulk of the people who have a PhD must acquire another one to three years experience under some type of preceptorship. I believe we do that superbly here. One of my concerns with predoctorates here is that with our present structure they do not complicate our life so that they minimize our capability of handling the post-doctorate. □

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synonym codons, each specifying the same amino acid, one species may emphasize three of these synonyms strongly, but weakly in the fourth. In another species of mammal, precisely the same sequences may be used for that amino acid, but the other two may be weak. The code is largely universal, and I think all living things on this planet will be found to use a similar code.

Synonym strength or weakness is the response of sRNA, that is, the formation of sRNA-ribosome-codon complexes or how much sRNA binds to the ribosome in response to a triplet. This response represents the sRNA concentration and how

TAB 74

MEDICAL RESEARCH AND HEALTH SERVICES*

James A. Shannon, M.D.**

It is a high honor and a most welcome opportunity to address this distinguished gathering on a matter that has occupied my attention increasingly in recent years. I refer to the general need and prospect for an improvement of the Nation's medical services through a purposeful extension of scientific knowledge and techniques.

A principle is emerging from intensive, responsible considerations of health care issues--the principle that every citizen is entitled to the best health services that the Nation's scientific and economic capability will permit. This is a good deal more than our citizen receives in the average health care situation, whether in the home or the physician's office, the hospital or the clinic. It is more than the individual physician or nurse, hospital or public health agency is prepared to deliver. For the principle--the goal--can only be attained through a broad movement, under inspired leadership, along lines as yet only visualized. Presently, however, I will describe a program, realistically planned and strongly implemented, which could be an effective spearhead.

There are compelling reasons for embracing this principle. For one, the ethics of the medical and allied professions do not permit lesser aims. For another, the missions of public-supported health programs, governmental

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* Alpha Omega Alpha Lecture, University of Pennsylvania, Philadelphia, April 1, 1966.

** Director, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

and voluntary, also demand high standards of service. A tax-supported research effort, like that of the National Institutes of Health, for example, has a responsibility for the effectual application of its sponsored results. Again, public demand is mounting for services of the quality found in our great medical centers--the teaching hospitals and the better independent institutions. And finally, there are general but no less urgent considerations both humanitarian and eccnomic, and the persuasive interests of national security and national pride.

The quality of health services and medical care has become a growing national issue. The people of this country are aware today as never before of the gradations in quality of services and care available--at one extreme, in our best medical centers and, at the other, in some of our communities where the medical practitioners are both professionally and geographically isolated. I hasten to add that many of the practitioners at the lower end of the gradient are nonetheless dedicated and may be simply too busy to do more.

As I view the trends in health care--say, from the end of World War II--several obstacles to optimum services clearly emerge. In general, the problem lies in the limited scope of interested organizations, for each has been unable to reach effectively beyond its traditional role or to promote a meaningful synthesis of resources.

The major obstacle to extending and improving our health services is the shortage of trained manpower. Clearly, the availability of personnel is the primary determinant of progress in meeting our health needs. A

realistic examination of the programs of Federal assistance for education in health fields is certainly in order. Are these authorizations commensurate with the demand and realistically pointed to the future?

A related concern is the enormous difficulty of providing for the re-allocation of highly specialized professional personnel. One of the most difficult questions of our time is how to skim off the excess supply of specialists in one field so as to permit their abilities to be used in another where the need is great. Our national effort, so far, has been to train more specialists for each set of problems as they arise--undoubtedly because we need more specialists in an increasingly technical, innovative society. But we should give serious thought to the possibility of developing more adaptable professional workers and providing stimuli that would lead to a re-allocation of resources.

A health manpower study, currently under way, will be of help in this issue. Constructive innovations, however, will call for many types of judgment.

A second important obstacle to the excellence of health care is its inadequate scientific base. Knowledge, techniques and equipment in health services at the community level are too frequently deficient--a result of the too limited sphere of influence of the great centers. The interface between optimum and mediocre must be shifted outward from the centers of excellence.

The inadequate scientific base of community medicine has many contributing factors, some of which subvert the efforts of the most conscientious workers. One is the inadequacy of systems for communicating new knowledge--that is, for the continuing education of physicians. To fill the gap, there is an excessive reliance on pharmaceutical advertising, a passive acceptance of the industry's products and practices. With respect to health care facilities, we must admit that our systems of accreditation are no guarantee of quality or modernity. The medical profession itself has gone far to raise standards of medical care through accreditation of schools and hospitals, licensure requirements, publications, group practice, and so forth, but has failed to overcome the major obstacles.

Our continuing efforts to broaden the base of fundamental knowledge must be sustained. There is much excitement in the scientific community these days; a great age of biology comparable to earlier flowering periods of chemistry and physics is foreseen. Just over the horizon, it seems, are broad theoretical concepts that will bring increasing order to the vast array of empirical observations now characteristic of biology and medicine. From these generalizations will derive more rational approaches to the complex problems that biology and medicine present. We must see that nothing impedes this process.

Moreover, there must be an acceleration of developmental research, bringing sound theory and observation to an applicable point and expanding the capabilities of practitioners and clinical units.

A third obstacle to optimum health care has been the limited availability and accessibility of services--again a problem of the restricted scope of interested groups. Voluntary health agencies are limited in their missions, funds and effectiveness. Federal, state and local health departments restrict direct services to patients--largely a matter of tradition. Physicians and hospitals are poorly distributed geographically. Thus, the utilization of existing health services should be improved, with realistic accommodation to their inherent capabilities and established roles.

As a fourth obstacle, I would list the high cost of health services, which again impedes progress toward universal excellence. Obviously, the average person cannot meet the costs of major illness out-of-pocket; and health insurance, Medicare, and other plans provide inadequate coverage. They neither ensure the protection of every citizen, nor enable health services and workers to do their best. Hospitals, for example, are burdened by rising costs, largely a result of increasingly complex technology.

To raise the quality of medical services will call for the application of more and more expensive resources. Costs under such conditions will strain our present framework for financing medical services and

care. New methods of financing, as well as new means for making the most of existing facilities, must soon be devised.

Are hospitals sharing high-cost facilities so as to utilize them fully? Is there a preponderance of small hospitals when there should be more comprehensive ones? Is enough effort going into research to cut the cost of expensive life-saving devices, looking toward savings over the long run? In view of the rising cost of labor in hospitals, is sufficient attention being paid to possible savings through automation? Does society allocate its resources in proportion to the severity of health and medical problems, or does it assign priorities by some other, perhaps wasteful system?

The fifth matter which I see as a major impediment to health progress--not quite parallel with the preceding--relates to human behavior and motivation. However successful the efforts to solve the problems of disease, however high the quality of medical care, the necessity will remain of getting people to take steps that would keep them healthy, that would get them through the doors of the doctors' and dentists' offices. The behavioral aspects of prospective patients have barely been explored. We must exert greater efforts to extend knowledge in this area. And we must consider the adequacy of health instruction in primary and secondary schools, and certainly at the higher educational level.

One final problem that confronts the health field today has emerged as a major challenge to science and medicine. I refer to the health hazards arising from the voluminous development and marketing of new products--foods, drugs and cosmetics. The regulatory function, primarily a responsibility of government, but actually shared by the ethical pharmaceutical firms, is making new demands on science. Prior to World War II, the protection of the public against hazardous drugs, adulterants, and economic poisons such as insecticides was not a matter for fundamental scientific attention. Science played an important part, but was quite equal to the task. Now there are serious challenges to science in formulating the necessary rules and procedures, for many unknowns and grave new hazards have come to the fore.

Better means must be found to assess the effects of long-term ingestion of drugs, additives, and environmental poisons so as to prevent cumulative biological injury. Unexpected properties of drugs, such as the causation of congenital defects, must somehow be predicted. Better control over the testing of drugs in the experimental stage, before approval for marketing is sought, must be achieved. And these problems must be resolved in such a way as to foster rather than retard the development of new products and technics over the vast range of foods, drugs and cosmetics. These are matters that challenge the fields of pharmacology, agricultural science, and broad realms of biology, as well as law enforcement.

Until the safety and efficacy of drugs and therapeutic devices are fully controlled, health services will be attenuated. Until related environmental health hazards are controlled--food additives, contaminants, air and water pollutants, and so forth--the Nation's health will be in jeopardy.

So what is needed, broadly speaking, to advance toward the goal I have proposed--the goal of equal and excellent health care for every citizen--is breadth of vision, and bold new approaches to supplement the old and to bridge gaps in the existing pattern of health resources.

There is no panacea, no single answer. The problems range from marketing practices in the drug industry to over-zealous surgery, radiation and medication; from hazardous hospitals to marginally qualified physicians and auxiliary workers; from prohibitive costs to grave shortages of competent manpower in both medical science and practice. But partial answers with a good probability for success have been instituted.

Recent Federal legislation, combined with new programs to administer the acts and funds to implement them, have been launched. These measures are far-ranging, and the problems of bringing plans into effective action are formidable. Here, then, is one general area in which imaginative leadership and collaboration can be fruitful.

Without going into detail, one might mention again the new Medicare program, effective July 1, to help meet economic needs. Also, a reorganization of the Food and Drug Administration is under way, promising a much

stronger regulatory operation. And there are Federal programs that will enhance universities and medical schools, offering solutions to the need for medical and scientific personnel, scientific facilities and special resources, and improved research management. Here are new horizons indeed for medical research and health services.

To promote the extension of medical excellence from the great centers to the wider community of practice, the National Institutes of Health has initiated its Regional Medical Programs. This operation is particularly relevant to the community hospital and to the improvement of medical care at the community level.

The main purpose is to provide the medical profession and medical facilities of the Nation with a better opportunity to make available the latest advances against the major diseases--heart disease, cancer, stroke, and related disorders. This overall objective is to be accomplished through the planning and establishment of regional cooperative arrangements among medical institutions. More specifically, these arrangements will serve as the framework for linking programs of research, training, continuing education, and demonstration activities in patient care, conducted by medical schools, clinical research institutions, and hospitals.

The principal means by which the Regional Medical Programs will seek to improve the quality of medical care is to ensure close contact between the development of new medical knowledge and technique and the delivery of high-quality patient care in the hospital environment. The operation

gives high promise of dealing with the paradox of more knowledge than we can handle--especially knowledge requiring the interpretation of highly trained specialists. And it offers a mechanism for bringing this knowledge to people on a grand scale.

Not to go into the mechanics of the program, I shall say in passing that grants will be awarded for the planning of a regional medical program and for the operation of pilot projects. According to the Act, the applicant must designate a local group qualified to advise in setting up the cooperative relationships among medical schools, clinical research institutions, and hospitals. A National Advisory Council on Regional Medical Programs, composed of outstanding leaders in medicine and public affairs, has been appointed, to advise the Public Health Service on policy and specific grant applications. The programs are not to interfere with the financing of patient care, or hospital administration, or professional practice. Clearly, the intent of the law is to build upon the already great capability of our medical institutions and personnel, over a three-year exploratory period.

This brief sketch of the major provisions of the legislation has indicated the overall program objectives and basic mechanisms. How will these be translated into actual operations, bringing to more people the latest advances in diagnosis and treatment of heart disease, cancer and stroke? The planning and implementation of program content will be up to the participating institutions. We expect and will encourage a diversity

of approaches, based on sound planning and orderly development, and addressed to the main objectives of better community medical care, continuing education of physicians, and extension of opportunities for research.

In general, then, there is great need in science and medicine for an integration of action programs to deal with the obstacles to optimum health. This movement should have the following attributes:

One, knowledge and technique must radiate outward from the center of excellence to the community, with feedback to promote research and teaching.

Two, the cost of health services, education and research must be met more equitably and realistically to remove the economic obstacles to a general high-quality of health care.

Three, these goals must be achieved without jeopardy to the freedom of scientific inquiry, professional education, or medical practice.

I hope my remarks have conveyed to you the conviction that a more meaningful integration of medical research and health services is possible--indeed, is in progress today--and offers a high potential for new conquests in the battle against disease. Nothing less than a bold

new attack is called for. This will be largely a furtherance of existing trends--the dynamic thrust of biomedical research, the wider application of its results, and the development of basic resources like facilities and manpower. But the movement also calls for initiative--for leadership, support and vision. Most of this must come from university centers, on the one hand, and from organized community groups, on the other.

TAB 75

Because you are members of one of the oldest and most highly-respected pharmaceutical companies and because you represent an important segment of that industry, I want to talk to you for a few minutes about the relationship between the pharmaceutical industry and the Federal Government in the field of medical research.

Questions about this relationship are being raised by various people in the industry who seem to have misgivings about the Federal Government's participation in disease-oriented medical research. About a year and a half ago, the Pharmaceutical Manufacturers Association issued a formal "statement of principle on public and private support of medical research" which took exception to some of the research activities of the Federal Government. During the past year objections were raised to an item which the Congress wanted to include--and did include--in the appropriation for the National Institutes of Health because one drug company, in particular, thought it inappropriate for NIH to take an active part in an important vaccine development program. The subject has been raised, in one

way or another, by a number of people who have come to see me or who have written to me or to my Congressional colleagues. I assume that you are also concerned because my Washington office has just sent me a copy of a paper which Mr. Powers, who takes a broader view, has written about the division of responsibility between government, the universities and private industry with respect to health research.

I want to comment on some of the specific points that have been raised in a moment. But let me first say something about the factors that have brought this question to the fore.

What seems to frighten some people in industry is the increasingly important role--let me be frank and call it the dominant role--which the Federal Government has come to play in the support of medical research. I am sure that you are all well aware of this but I want to cite a few figures to give you some quantitative measure of what has happened to the pace and scope of our national medical research effort since the beginning of World War II.

Twenty-five years ago our total national expenditure on medical research was less than $50 million. Over half of this amount was provided by and spent by industry--mainly the pharmaceutical industry. The Federal Government's investment in health research was only $3 million, or about 7% of the national total.

Today our national expenditure on medical research is rapidly approaching $2 billion and about two-thirds of this amount is provided by the Federal Government.

The growth of Federal support for medical research has been particularly significant during the past eight years because the amounts involved have at last become substantial enough to be effective. Since 1957, the Federal Government's investment in the future health of the American people has increased almost five-fold--from $229 million (in 1957) to nearly $1.2 billion (in 1965).

The reason for this dramatic increase is very simple.

... The American people believe that health is important.

... They believe that the war against disease and physical and mental disabilities is one of the major tasks facing this nation.

... They are determined that the full capability of modern science and technology should be brought to bear on this task.

... They believe that the investment of public funds in so vital an activity will benefit them personally and is clearly in the national interest.

The Congress shares these views and has responded to the public demand for a vigorous medical research effort. I am proud to have been able to play an effective part in providing Federal support for such an effort. I don't think that the rapid increase in Federal funds for medical research is something for which I--or anyone else--need apologize.

Now let me draw your attention to an important fact that is often over-looked. The substantial increases in the Congressional aopropriations for medical research are not a measure of the growth of the Federal Government's direct participation in medical research. Actually, about 60% of the Federal funds are used to make grants to educational institutions and other non-profit organizations. In fact, half of the total annual expenditure of our medical schools

is contributed by the Federal Government in the form of research grants and contracts and training grants.

Although the Federal Government provides two-thirds of the money spent on medical research in the United States, the Federal Government's own laboratories and other research installations spend less than one-fifth of the national total.

Let me cite a specific example. The appropriations for the National Institutes of Health increased almost five-fold between 1957 and 1965--from $213 million to $1,059 million. But the amount included in these appropriations for NIH's own research program was $34 million in 1957 and $77 million in 1965--which is just a little more than double. If you take account of the salary increases granted to Federal employees during this period and the general rise in operating costs, it becomes clear that the expansion of the direct research activity made possible by this increase is actually very modest.

Obviously, the Federal laboratories are not taking over the lion's share of medical research work in this country.

What the Congress has tried to do is to escalate the war against disease. It has done this mainly by making substantial funds available to non-federal institutions for the conduct of research, the construction of research facilities, and the training of research scientists.

I have quoted those figures to indicate the extent of the Federal Government's commitment to the support of medical research. They are relevant to, but do not answer, the questions raised about the relationship of Federal research activities to those of the pharmaceutical industry.

One of the principal points at issue is not the level of Federal research activity but its aims and direction. The Pharmaceutical Manufacturers Association expressed its view quite clearly. It suggested that "the primary role of government in medical research is to encourage the expansion and enrichment of the flow of fundamental knowledge, sometimes referred to as basic research"--that is a direct quotation. On the other hand, it stated that the "role of the pharmaceutical industry is the application of basic knowledge from all sources to the discovery and design of new medicines."

I think the PMA must have realized that this definition of functions might give someone the impression that it was suggesting that the government should confine itself to research that has no immediate pay-off and should leave to the industry any project likely to lead to a marketable commodity. The statement, therefore, went on to say that "The industry recognizes it too has an obligation to contribute to the store of fundamental knowledge, but the depth of this responsibility differs from that of institutions primarily dedicated to the exploration of the unknown."

The Congress recognizes the fundamental importance of fundamental research and has consistently made provision for its support. A high proportion of the grants made by NIH are for basic research projects. Much of the health research facilities construction funds are used to build laboratories in which basic research will be done. One of the purposes of the General Research Support program, under which awards are made on a formula-basis to health professional schools and now also to university departments, is to enable

these schools to support fundamental research that might not be able to compete for a regular project grant from one of the categorical Institutes. Two years ago the Congress gave further evidence of its commitment to the support of basic research by creating the National Institute of General Medical Sciences.

The Congress has also made ample provision for building up what Mr. Powers has called the "infra-structure" for research--particularly in the training of research personnel. Each of the nine categorical Institutes devotes a substantial portion of its appropriation to training grants, fellowships, and the important new Research Career Development Awards.

But let me make one thing very clear. The primary purpose of the Federal programs is to wage war on disease and not to support some particular kind of research. The public and the Congress are interested in promoting better methods for preventing, diagnosing and treating diseases. All possible approaches towards this goal must be fully exploited. It is certainly not in the national interest to

lay down artificial restrictions on the activities of one or another segment of the national research community or to engage in self-interested jurisdictional disputes about who should be allowed to do what.

In setting up the National Cancer Institute, the first of the present constellation of categorical Institutes at NIH, the Congress gave it the task of doing whatever is necessary to conquer this dreadful disease. The Act explicitly states that the Institute was created for the purpose of:

> "conducting researches, investigations, experiments and studies relating to the cause, diagnosis and treatment of cancer; assisting and fostering similar research activities by other agencies, public and private; and promoting the coordination of all such researchers and activities and the useful application of their results, with a view to the development and prompt, widespread use of the most effective methods of prevention, diagnosis, and treatment of cancer....."

You will note that "conducting research" is listed as the Institute's first task--and this research is described as relating equally to cause, diagnosis and treatment.

The Acts setting up the other Institutes use much the same language.

Nowhere in the legislative history of these Institutes is there any suggestion that they should confine their direct research activities to fundamental research. On the contrary, the initial intent of Congress was that these Institutes would devote themselves to direct attacks on the major diseases which they were set up to combat. It was only in subsequent years that the Congress came fully to appreciate the long-range importance of fundamental research. The NIH programs specifically for the support of fundamental research are all of fairly recent origin.

No distinction can be made between the role of a Federal and an industrial laboratory on the basis of the kind of research it should do. Each must be free to make the fullest use of the special competence of its scientific staff and its research resources and--above all--to exploit new ideas and new approaches. Isn't that the way the

scientific community has always approached its task? Isn't that the surest road for the most rapid progress?

Some people in the pharmaceutical industry apparently don't think so. This was demonstrated, in a most disturbing manner, in connection with the wish of the Congress to stimulate work on a German measles vaccine.

The urgent need for such a vaccine is obvious.

... The severe 1964 epidemic of this disease among pregnant women is thought to have resulted in the birth of as many as 20,000 defective babies. It is feared that the epidemic on the West Coast earlier this year will have equally tragic consequences.

... Statistics gathered in NIH's Perinatal Study indicate that one pregnant women out of three is exposed to German measles. I am told that it is possible to be infected merely by standing beside an infected person in a super-market check-out line.

... Twenty percent of the women of child-bearing age in the continental United States have <u>not</u> acquired an immunity to German measles. In Hawaii and

> Puerto Rico 60% are <u>not</u> immune. Most women do not know whether or not they are immune and therefore have a constant anxiety when they are pregnant. ... The risk of having a defective child is as high as 50% if the mother is exposed to rubella during the first month of pregnancy.

You know better than I do the difficulties encountered in trying to develop a German measles vaccine--and the dangers involved in testing such a vaccine.

Among the many people working on this problem are several scientists at NIH. One of these scientists--Dr. John Sever--developed the first experimental German measles vaccine to be successfully tried on adult volunteers. Efforts to duplicate this vaccine commercially have not been successful but it seems obvious that the work of this group should be encouraged. Yet an official of one of our major pharmaceutical companies made strenuous efforts to persuade Congress to curtail the work of the NIH group which he felt should be left to scientists in his company's staff who were also working on the problem.

I am happy to say that a number of eminent scientists opposed this move which I regard as blatantly self-interested and unprincipled.

The principle on which we must proceed was well put by Dr. Sabin in his telegram to the Congressional committee:

> "When solutions are in sight for urgent public health problems but, as in the present case, much research remains to be done, humanitarian scientists must pool their efforts and work cooperatively to hasten the day when their knowledge can become useful in alleviating human suffering.
>
> "The people of the United States and of the world are entitled to the competence of all available scientists and not just those in a private company."

That is a view with which I can heartily agree.

The whole history of vaccine development is one of cooperative action in which government laboratories and non-profit foundations have been as deeply involved as any private firm. In fact, the pharmaceutical industry has rarely been in the forefront of the initial development.

It has usually taken over from national agencies after the technology had been developed and the risk of failure had been substantially reduced.

... The yellow fever and typhus vaccines, which gave almost perfect protection against these diseases in World War II, were developed by the Rockefeller Foundation and NIH.

... The vaccine for Rocky Mountain Spotted Fever, which removed a major hazard from a large area in the West, was developed by NIH.

... The polio vaccines were developed by Dr. Salk and Dr. Sabin with the support of the National Foundation.

... The influenza vaccine was the work of the Rockefeller Foundation.

... The new measles vaccine is based on a virus strain developed by Dr. John Enders. From whom?

In each of these cases the pharmaceutical industry has improved and modified the vaccines developed by scientists in other sectors of the research community. Such cooperative action is clearly in the public interest--and it has not hurt the industry.

The pharmaceutical industry has a more impressive record in the development of drugs. But even in this field the industry owes a debt to other scientists--as, for example, for the first antibiotics and for the discovery of the psychological effects of compounds in use for other purposes.

One might also ask whether the pharmaceutical industry would have been willing to tackle so costly and tedious a search for effective new drugs as that of NIH's cancer chemotherapy program.

No part of medical research should be the exclusive province of any segment of the scientific community. Steady progress in the age-old battle against disease demands the best efforts of all who can make a contribution.

The areas of potential conflict between private profit and public benefit will remain--in fact, they may well grow larger. The development of the artificial kidney, work on a replaceable artificial heart, the automation of laboratory procedures and of patient monitoring, and other innovations in the field of bio-engineering all depend on the application

of industrial engineering skills and technical competence but they are also likely to be heavily dependent on Federal support.

It is neither possible nor desirable to attempt to assign fixed roles to scientists in the universities, in the Federal Government, and in industry. What is needed is cooperation towards the achievement of a common purpose. A congenial mix of different skills, different outlooks, and different research environments is a national asset, not a hinderance.

There are problems in these relationships. I agree, for example, that the Federal Government must adopt a realistic patent policy which will encourage capital investment by industry and which will protect the public interest without penalizing industry for cooperating in important joint ventures. But the solution for these problems is not that everybody should try to go their separate ways.

In view of the great humanitarian task of medical research, I hope that all those engaged in it can continue to work together in a spirit of goodwill. With Christmas only ten days away, that wish is a good note on which to end.

TAB 76

Statement by Dr. James A. Shannon
Director, National Institutes of Health
Before the Senate Committee on Commerce
Wednesday, May 25, 1966

Mr. Chairman and Members of the Committee:

We appreciate this opportunity to express our views on S. 2322 as modified in Committee Print No. 3. Let me reiterate that we share the Committee's concern regarding humane treatment of animals. We know the Chairman and all the members of this Committee are deeply interested in developing constructive and responsible legislation in this complex field. We hope we can be of assistance to the Committee in this task. We are deeply grateful to the individual members of this Committee for the strong support that many of you have given to Federal support for medical research and for programs that would bring the benefits of this research to the American people.

We agree with the purposes of the bills being considered by the Committee, including Committee Print No. 3 of S. 2322. We are convinced there is a need for legislation to regulate interstate commerce and transportation of dogs and cats for medical research and to provide for establishment of standards for laboratory animal care in research facilities. Both needs have emerged clearly in recent years. They stem largely from the growth in medical research that has taken place in the past ten years. In fiscal year 1955, the national expenditures for medical research totalled $261 million. Today the total national expenditures on medical research are about $1.9 billion, of which the Federal Government's expenditures account for about two-thirds.

This rapid growth in a relatively short period of time has substantially increased the need for laboratory animals. In our view, the allocation of resources for laboratory animal production, procurement, mangement and care has not kept pace with this growth in the need for animals. Faced with pressures to expand their physical facilities in research and health manpower development, the universities, the medical schools and related institutions have tended to give animal facilities a lower priority. Given the choice of allocating their funds for research laboratories, classroom buildings, or other facilities versus using these same funds to modernize or remodel animal facilities, many institutions chose the former as being higher priority projects. Similarly, systematic efforts to develop or expand the reservoir of properly trained subprofessional and professional personnel required to handle laboratory animals has not taken place on a scale commensurate with the expanding needs.

This situation is not unique to animal care. As you know, grave concern is now being expressed about health manpower shortages and about the need to modernize the Nation's hospitals. About one-third of our hospital beds are in hospitals that need to be completely replaced or undergo major renovation.

The need to improve the facilities for the care of laboratory animals was indicated in a study published in March 1964 by the Institute of Laboratory Animal Resources of the National Academy of Sciences-National Research Council. The report, entitled Animal Facilities in Medical Research, was based on a survey conducted by a committee of the Institute and covered

the examination of laboratory animal facilities, space, equipment, budget, personnel and training in 561 nonprofit, nonfederal, medical research institutions in the United States. Fifty-eight of these institutions were site visited by highly qualified professional personnel and 503 institutions supplied information through mail questionnaires. The data reflect conditions in the years 1960 and 1961. The survey revealed that "a majority of those (58) institutions site surveyed were in need of renovation or new construction. Renovation needs included surfacing of walls and floors, installation of better ventilation and air handling equipment, enlargement of sewer drainage and reduction of animal population density in some areas." Although these data are over 5 years old, and conditions have unquestionably changed, we are still convinced that a substantial proportion of research facilities will have to have funds for construction and renovation if they are to comply with the standards likely to be prescribed under Federal legislation. Research institutions are generally non-profit organizations, and without Federal assistance in upgrading their facilities so they can comply, these institutions would be forced to divert needed funds from important research, which might save many human lives.

The members of this Committee are familiar with some of the great advances in medical knowledge which have taken place in recent years, such as the broad advances in vascular surgery, in heart surgery including the complex procedures involving the open heart, development of the artificial kidney, management of trauma and shock encountered in war

injuries and serious accidents, and the development of many drugs for the management of high blood pressure, heart attacks and other disorders.

Most of these advances have in common their dependence on the use of large numbers of animals in research. The advances in research on heart surgery, for example, are very dependent upon the availability of large numbers of dogs observed over long periods of time under conditions that support the health and vigor of the experimental animals. Thus, we feel very strongly that the question of proper care and treatment of laboratory animals is an integral part of the conduct of much, if not all, medical research.

The Department, in the Public Health Service and the Food and Drug Administration, has attempted to develop its facilities and animal research and care programs as a model for other biomedical research institutions. We have in the National Institutes of Health developed facilities and resources which have been used by many other institutions in the design, construction, and maintenance of animal facilities and systems for managing and care for laboratory animals. In 1962 we established an Animal Resources Branch in the Division of Research Facilities and Resources to serve as a focal point for identifying and meeting the requirements for animal facilities and resources in the grantee institutions. The Branch administers research grants directed at such problems as improving animal care techniques, diseases of laboratory animals and improved diagnostic services for detecting diseases of laboratory animals. The Branch also gives technical assistance to grantees in the organization of laboratory

animal programs and in the design of facilities. The staff of the Branch participates in the review of applications and plans submitted to the NIH for the construction of laboratory animal facilities under the Health Research Facilities Construction Program. From 1957 (the year in which the Health Research Facilities Program was inaugurated) to the present time, NIH awarded 115 matching grants totalling $24.1 million for construction of laboratory animal facilities. These grants have made possible construction of animal facilities costing $55.6 million. About half of this amount was awarded during the past three years for facilities which therefore are not yet completed for the most part. (It normally takes about three years from the time an award is made until facilities are completed and in use.)

The Public Health Service also contracted with the Animal Care Panel, a nonfederal group of professional persons interested in laboratory animal care, to develop "A Guide for Laboratory Animal Facilities and Care," which contains sound guidelines for the care of laboratory animals. This Guide was recently revised under the auspices of the Institute of Laboratory Animal Resources of the National Academy of Sciences-National Research Council. It is currently sent to each recipient of an NIH research grant and is followed in the animal units within the Public Health Service and the Food and Drug Administration. The Guide covers the qualifications of personnel, materials and design for facilities, biological safety, and animal care procedure. I would like to include a copy of the Guide for the record. We are confident it

can serve as initial basis for the development of federally prescribed standards for laboratory animal care. At the same time, we are aware that reliable standards for certain species of animals have not yet been developed, and research is needed to develop them.

In addition to being officially distributed by the Public Health Service as a guide for its grantees, the "Guide for Laboratory Animal Facilities and Care" is also used by the newly established American Association for Accreditation of Laboratory Animal Care in the new program of voluntary accreditation of laboratory animal care facilities. Among the sponsors of this program are the American College of Physicians, American College of Surgeons, American Association for the Advancement of Science, American Hospital Association, American Medical Association, American Dental Association, Association of State Universities and Land Grant Colleges, American Veterinary Medical Association and the Association of American Medical Colleges. The program, which is similar in operation to the hospital accreditation program of the Joint Commission on Hospital Accreditation, is the outgrowth of earlier activities by the Animal Care Panel.

The Animal Care Panel also has undertaken, through its local branches, a program of Laboratory Animal Technician Training and Certification. This program was launched in recognition of the necessity for having well-trained animal handlers to provide quality laboratory animal care. With sufficient support it could be expanded rapidly to satisfy an unquestioned national need. Two of the Institutes of the National Institutes of Health also have supported specific research-oriented

training programs in laboratory animal medicine. These programs have provided postdoctoral research training for a limited number of laboratory animal specialists.

I have described these activities of the Department primarily to demonstrate that our deep concern for proper care and handling of laboratory animals is not new. But we are now convinced we cannot deal adequately with the problem without additional appropriate legislation.

From this general background I would like to turn to the legislation under consideration by this Committee, namely, Committee Print No. 3 of S. 2322. Several issues are raised by this bill which concern the DHEW. First; the bill combines under one legislative authority two matters which, in our view, should be treated separately: (1) the regulation of transportation and sale in interstate commerce of dogs, cats, primates, guinea pigs, rabbits and hamsters; and (2) the licensing of all research facilities on the basis of standards for humane care and handling.

The Department of Agriculture would be an appropriate agency to regulate interstate transportation and sale of animals; we hope that any such legislation would be limited to the transportation and sale of dogs and cats. We are confident this approach would eliminate any abuses in procurement of these animals that may exist. We do not believe that transportation and sale of guinea pigs, hamsters and rabbits pose problems requiring Federal regulation and to include these other kinds of animals will add to the expense of administration for all parties concerned.

The Committee may therefore wish to consider whether there is sufficient evidence to justify the additional costs and administrative burden involved in the record keeping, inspection and licensing procedures for these animals.

There is now pending before your Committee H.R. 13881 which the House of Representatives has passed and which is limited to regulating transportation and sale of dogs and cats intended for research. We would hope that any legislation reported out by your Committee would be similarly limited.

We strongly urge that the inclusion of research facilities, as proposed in Committee Print No. 3, be omitted. There are several reasons for our recommendation.

First, the proposal to license research institutions (including educational institutions) is, in our judgment, both unnecessary and undesirable. The sensitive relationships between the Federal Government and institutions of higher education are a matter of continuing concern, both to the institutions and to the Federal Government. With the increase in the number of institutions receiving financial support from the Federal Government, particularly in programs funded by the Public Health Service and the Office of Education, we have been careful to structure our relationships so as to keep to the essential minimum Federal regulation of educational institutions. We feel the licensing provisions of this bill would set an unwise precedent in relationships between the Federal Government

and the universities. Moreover, we do not believe licensing is necessary to assure that research facilities achieve reasonable standards of laboratory animal care. The best way to accomplish this, in our judgment, is the kind of accreditation procedure with which educational institutions in particular are familiar. Accreditation would provide an overall mechanism for inspecting facilities and insuring compliance with standards. Such a mechanism is embodied in a bill introduced by Senator Hill, S. 3332, which has been referred to the Committee on Labor and Public Welfare.

Second, the definition of research facilities contained in Section 2, paragraph (f) of Committee Print No. 3 is so broad that it would encompass perhaps 7,000 facilities in the United States. There are about 2,000 research facilities receiving Federal grants and contracts for biomedical research involving animals. But by including all establishments using rabbits, guinea pigs, and hamsters for tests, it will be necessary to include a large number of hospitals, private clinical pathology laboratories, pharmaceutical and other industrial laboratories, state testing facilities, and many secondary and undergraduate schools. This will add at least 5,000 establishments to be inspected and licensed, thereby greatly complicating administration and increasing costs.

A third point of concern raised by Committee Print No. 3 relates to the need for additional Federal funding required by the imposition of standards of laboratory animal care, if federally supported research is to be continued at its present and projected levels. The introduction of standards for laboratory animal care to which all research facilities

would be required to adhere will generate requirements for construction and renovation of animal facilities which we estimate will cost about $100 million. Substantial additional Federal, as well as local, resources will be needed to meet these requirements. S. 2322 does not offer a way for the Federal Government to assist in meeting these needs for improved facilities.

Fourth, Section 11 of the bill would authorize inspectors to confiscate or destroy animals found to be suffering as a result of a failure to comply with standards. It would appear that the judgment of whether an inspector was authorized to confiscate or destroy animals being held by research facilities would rest with him rather than with the research facilities. The operational distinction between animals merely resident in research facilities' animal quarters from those undergoing actual research and experimentation is, in my opinion, at times impossible to make by anyone other than those in charge of the research facilities. This provision of the bill is ambiguous and could be quite troublesome.

Finally, we believe it would be much more appropriate for the Department of Health, Education, and Welfare to have primary responsibility for legislation involving such significant relationships with the medical and educational community. HEW is already administering programs to expand health research facilities and resources for training of professional laboratory animal personnel, for research on laboratory animal care, and for overall improvement of laboratory animal resources. Humane care and

treatment of laboratory animals is intimately related to all other aspects of laboratory animal resources. It is in the interests of the medical research community to have access to adequate numbers of healthy laboratory animals and the introduction of standards for laboratory animal care would facilitate achievement of this objective. But an effort to improve laboratory animal care through establishment and enforcement of animal care standards must, for the reasons I have already outlined, be coordinated closely with programs to expand facilities and resources to facilitate orderly achievement of these standards without jeopardizing important programs of medical research and education. We feel that this Department, with its resources and relationships in every area of health and medicine, can most effectively carry out the intent of Congress and should, therefore, be responsible for administering the program.

We want to emphasize that in our view there is a necessity for establishing national standards for laboratory animal care to be met by all institutions as a condition for receiving Federal support for research involving the use of animals. We fully support the bill recently introduced by Senator Hill (S. 3332). It would require all institutions receiving Federal support for medical research involving the use of animals to comply, within a reasonable time, with standards prescribed or approved by the Secretary of Health, Education, and Welfare. The bill also would require each research institution to establish a formal committee of qualified scientists to review policies and procedures covering the care and use of animals in the institution's research program.

In establishing standards for care under S. 3332 the Secretary would be required to consult with other interested Federal agencies. The standards would apply to Federal laboratories as well as to nongovernmental research facilities. S. 3332 would also amend section 706(a) of the Public Health Service Act to authorize up to 25 percent of the appropriation for construction of health research facilities to be used for grants to pay up to 66 2/3 percent of the cost of construction or renovation of laboratory animal facilities in research institutions. In addition, the Department of Health, Education, and Welfare would make use of existing legislative authorities to stimulate the training of personnel needed to staff laboratory animal facilities. Existing authorities in the PHS Act will be used to train professional personnel;For subprofessional personnel, we will use the authority contained in the Manpower Development Training Act, administered by the Department of Labor.

In addition to providing for humane care and treatment, S. 3332 would provide the basis for much-needed expansion and support of laboratory animal resources to assure that these resources keep pace with the expanding needs of the medical research community for adequate supplies of healthy laboratory animals. Under S. 3332 the whole program would be administered under the leadership of HEW, the agency most concerned with development of adequate animal resources. It would be coordinated with plans to increase the training of animal caretakers and professional laboratory animal personnel, as well as to increase research on laboratory animals. The laboratory animal program would be an integral component

of the overall biomedical research program. We feel this is a workable, reasonable, overall approach to the animal care problem which can and will produce results consistent with the concern of Congress in considering needed legislation in this area.

In summary, we feel that the theft of dogs and cats and their care and handling by dealers and during transportation can best be handled through a bill along the lines of H.R. 13881; that is, one limited to regulating the transportation and sale of dogs and cats for research purposes. Separate, complementary legislation should be enacted to govern the care and handling of laboratory animals by research and educational facilities. We support S. 3332 for this purpose.

TAB 77

NOTES FOR JUNE 1 SPEECH

New York University

Theme

The state of medical science is such now that in certain well-defined areas it is feasible to launch large target-type programs of which the objectives can be clearly defined. Up to now NIH has been conducting these under the rubric of collaborative studies. The experience with the Cancer Chemotherapy Program and Perinatal Study has been disappointing in some respects--namely, the tendency to lose focus on the primary objectives and to meet criticism of the high cost and slow yield. But these programs, it should be understood, have been undertaken in the face of known impediments.

Historically, the massive attack has never been a howling success. One of the more notable programs of this type was malaria screening and human trials in the World War II period and the success of this effort was largely attributable to the wartime impetus.

The impediments are that scientists resist strong central direction feeling that this is incompatible with the broader scientific approach and there is the tendency to avoid mechanical and routine operations. Criticism is often concerned with the high cost of these programs which is inescapable in view of the large numbers of observations encompassed. Hence, studies of this type that NIH will undertake in the future, perhaps directed toward development of vaccines and artificial organs, must

incorporate 4 criteria: (1) the objective must be feasible and clearly defined, (2) focus on this objective must be routinely maintained, (3) experimental design must conform to sound biometric principles with assurance that the data will be sufficient for the desired conclusions, and (4) high cost must be anticipated.

Target-type programs may be of several kinds and generalizations are difficult beyond a point. One type seeks information through observations on large masses of data (Perinatal Study). Another is concerned with broad screening of drugs and the like and, while it may involve mass data processing, the emphasis may be on quality of performance throughout the screening process. Another type involves engineering development and high quality individualized performance is again emphasized with coordination of effort being a difficult aspect.

The mechanisms for research support as developed by private foundations and government agencies have been conducive to undirected inquiry of the type ordinarily supported by grants. Here the performer is usually the academic scientist of the nonprofit private institution. In the target-type program on the other hand, it is often necessary to seek the resources of industry where the profit motive is a primary incentive. Thus, the controls over the support system must be of a different kind; the instrument of the contract is usually evoked; and problems may arise with respect to patents, conflict of interest, etc. Thus it is necessary for government agencies seeking this type of program in biomedical science to evolve new support machinery.

TAB 78

REMARKS*

DR. JAMES A. SHANNON

DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH

Mr. President, we are all pleased with your interest in and concern with the progress of medical research. This Nation now leads the world in the extent of scientific effort directed toward problems of health and disease. We are gravely conscious of the role that the programs of the National Institutes of Health have served in this development.

As the major research arm of the Public Health Service the NIH has as its mission the advancement of the health and wellbeing of the American people through scientific effort. To this end we have engaged the scientific community of the Nation in pursuit of:

. . . A greater understanding of the biological and behavioral phenomena that underlie disease, disability and health.

. . . The advancement of our capability to diagnose, treat and prevent disease and to maintain health throughout man's life span.

. . . The effective movement of new knowledge and technology from the centers of scientific and academic medicine to the community health service framework.

The framework for our quest of these goals is the several National Institutes which were created by legislation to foster the scientific

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* Meeting with the President, June 27, 1966.

attack upon the major disease and health problems. There are now nine of these Institutes whose budget proposals for fiscal year 1967, together with the funds for related NIH activities, aggregate $1.3 billion. The size of the individual Institute programs is reflective of the relative magnitude and seriousness of the health problems with which they are concerned and the stage of development of our research efforts in these areas. (Chart I)

The conduct of these programs involves the performance of several functions. First, the support of research in the universities, medical schools, hospitals and other research institutions through grants-in-aid and the conduct of research in the laboratories and clinics of NIH at Bethesda and its field stations. Second, the training of specialized manpower through fellowships and training grants to provide for our future teaching and research capability upon which continued progress in health is dependent. Third, these activities are complemented by a program of research facilities construction and programs providing for the stability and further development of our academic and research institutions. These are integral and vital components of our national effort. Lastly, our concern with the problems of bringing research progress to bear upon health practice and the delivery of services is particularly evident in the newly inaugurated Regional Medical Program and the Community Mental Health Center program. (Chart III). These latter activities complement parallel activities in the Bureau of State Services of the Public Health Service.

The support of medical research has had as its first objective the building of a productive national medical research system with broad and sophisticated capability. The vigor and growth of this foundation continues to be a matter of vital concern since the state of knowledge relevant to health and disease is still much too inadequate to permit any relaxation or diminution of this support. The second objective is to reach deeply and continuously for opportunities to exploit advances in knowledge where this can be achieved by directly organized activity. Thus the deployment of our national resources in the medical sciences is divided between that which advances the base of science as determined by the consensus of the scientific community and the effort directed towards the systematic exploitation of selected target areas. It is estimated that in 1966 this Nation will spend from both public and private sources approximately $2.1 billion for medical research activities. In rough terms approximately $1 billion will go to sustain and advance the scientific base while $1.05 billion, or a little over 50 percent, will be specifically utilized in targeted attacks upon major problems or disease objectives. (Chart III).

Such a distribution in the deployment of resources is apparent in the programs of each of our Institutes. Progress in the medical sciences made possible by the substantial investment in the scientific base in the postwar years is now yielding important additions to knowledge, greater insight into disease problems and making possible the development of new

techniques and devices. Thus opportunities are increasingly available for more purposeful exploitation of our advancing scientific and technical capability in the interest of better diagnosis, treatment and prevention of disease. This circumstance is reflected in the distribution of our research funds in the several Institute programs between that scientific activity determined by scientific consensus to be important and relevant to the respective disease areas and the research efforts being undertaken as a part of organized programs. (Chart IV).

This process confronts us with the difficult and complex task of making sound choices amongst possible areas of target research. This task is difficult because our scientific understanding of life processes is gravely incomplete. Thus new knowledge may change radically the direction of further research. In a setting of such uncertainties one must accept the risk of expending large sums of money upon leads and ideas which may eventually turn out to be unproductive. But despite this limitation we believe there are clear opportunities for additional intensive research efforts. These range from the possibilities associated with artificial organs, such as the artificial heart and the artificial kidney, to the exciting pursuit of the relationship between viruses and cancer. An enumeration of our current target efforts and the possibilities of further systematic research activity can be portrayed by the several Institute Directors. (Institute Charts).

We are gravely conscious of the obligation imposed by the generation of new knowledge to provide for its rapid availability and application in the diagnosis, treatment, and prevention of disease. Two major events will

contribute significantly to this process. Both of these are the result of passage of legislation during the course of this Administration. The first of these is the program for construction and staffing of community mental health centers which will permit abandonment of the medieval concepts of banishing the mentally ill to large asylums and bring mental health services to the midst of the community health scene. The second is the passage of legislation establishing the Regional Medical Programs which will forge the essential link for the movement of the advances generated in the centers of scientific and academic medicine to the community scene, its hospitals, its health services, and its practitioners.

This brief summary review of our programs and their character, Mr. President, I hope will provide you with a setting in which you can pursue your specific concerns for the furtherance of the health of the American people through reaping the progress that research can bring.

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